# The NORTH CAROLINA MEDICAL JOURNAL

THE NINETY-SECOND ANNUAL SESSION
WILL BE HELD AT PINEHURST
MAY 1, 2, AND 3

Vol. 7 February, 1946 No. 2

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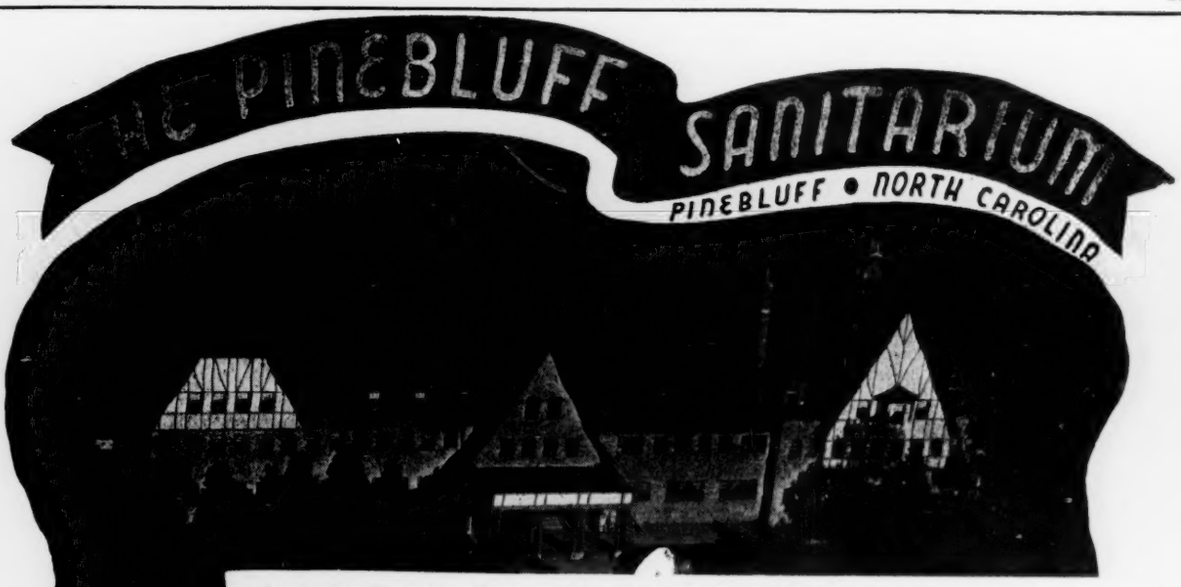


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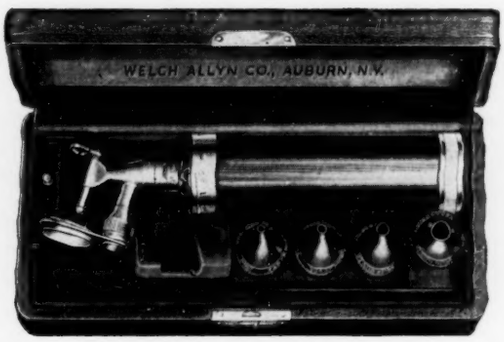


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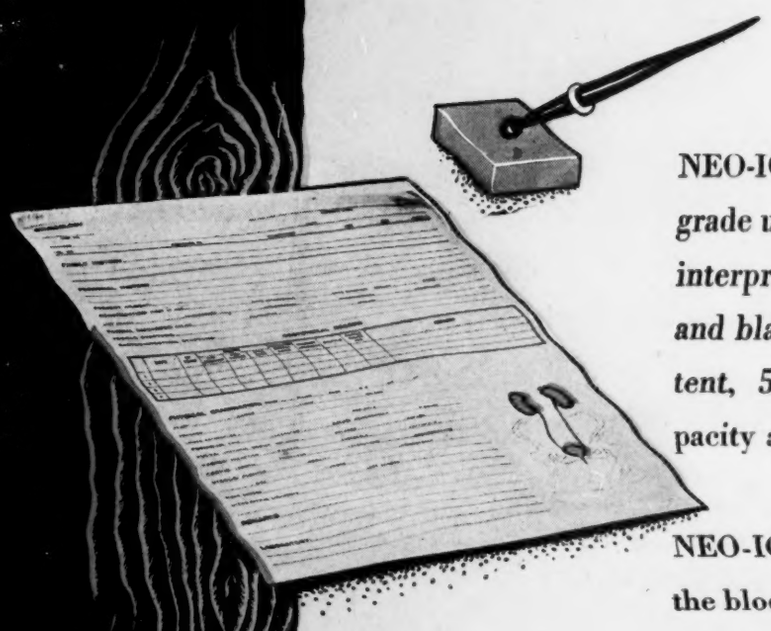

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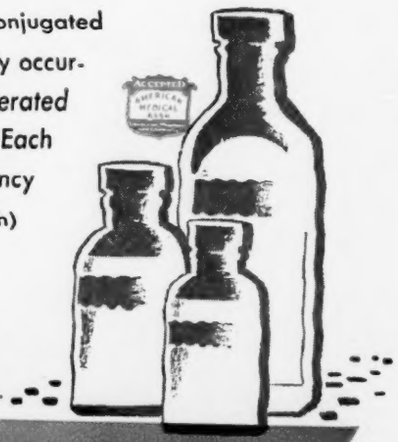

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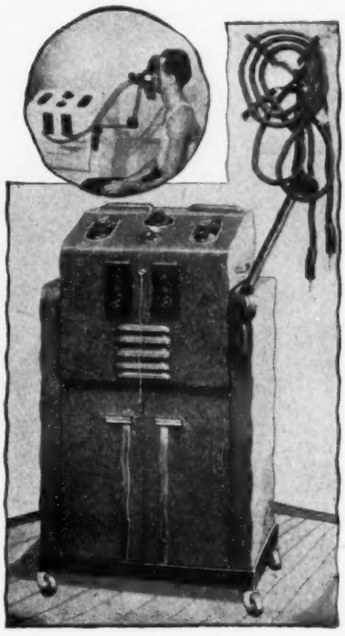

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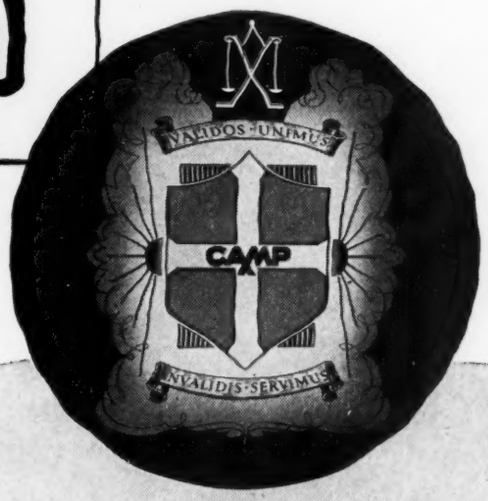


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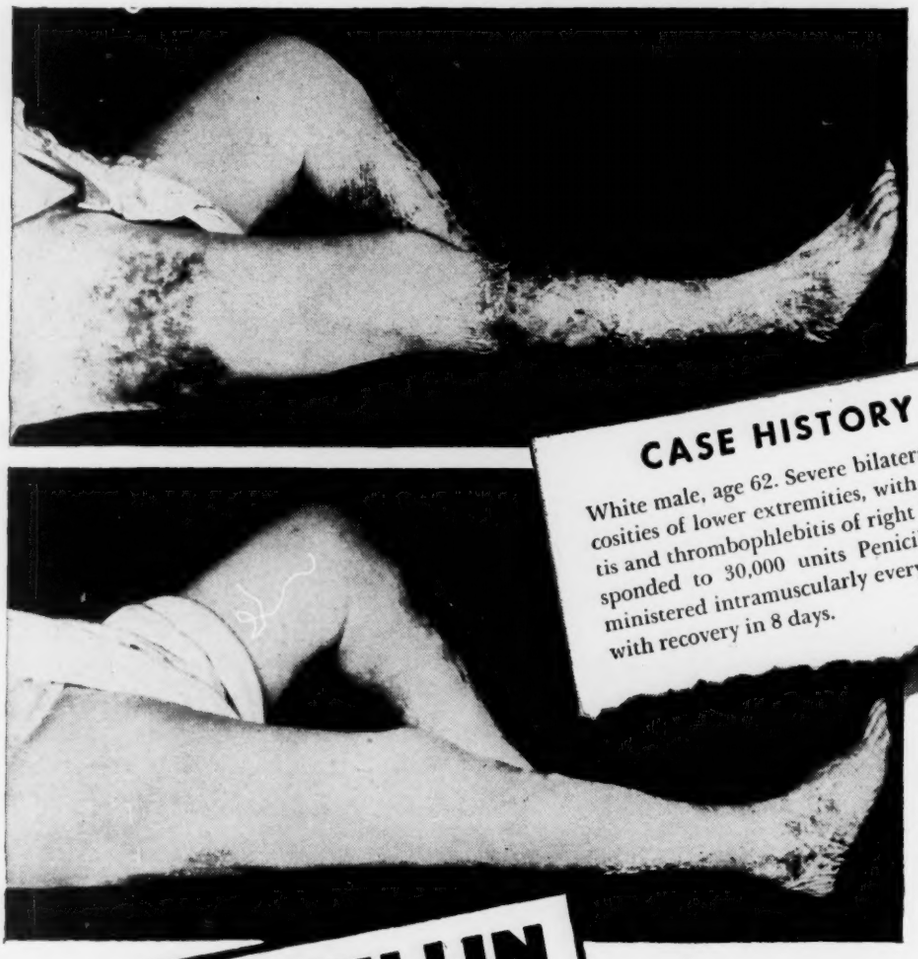

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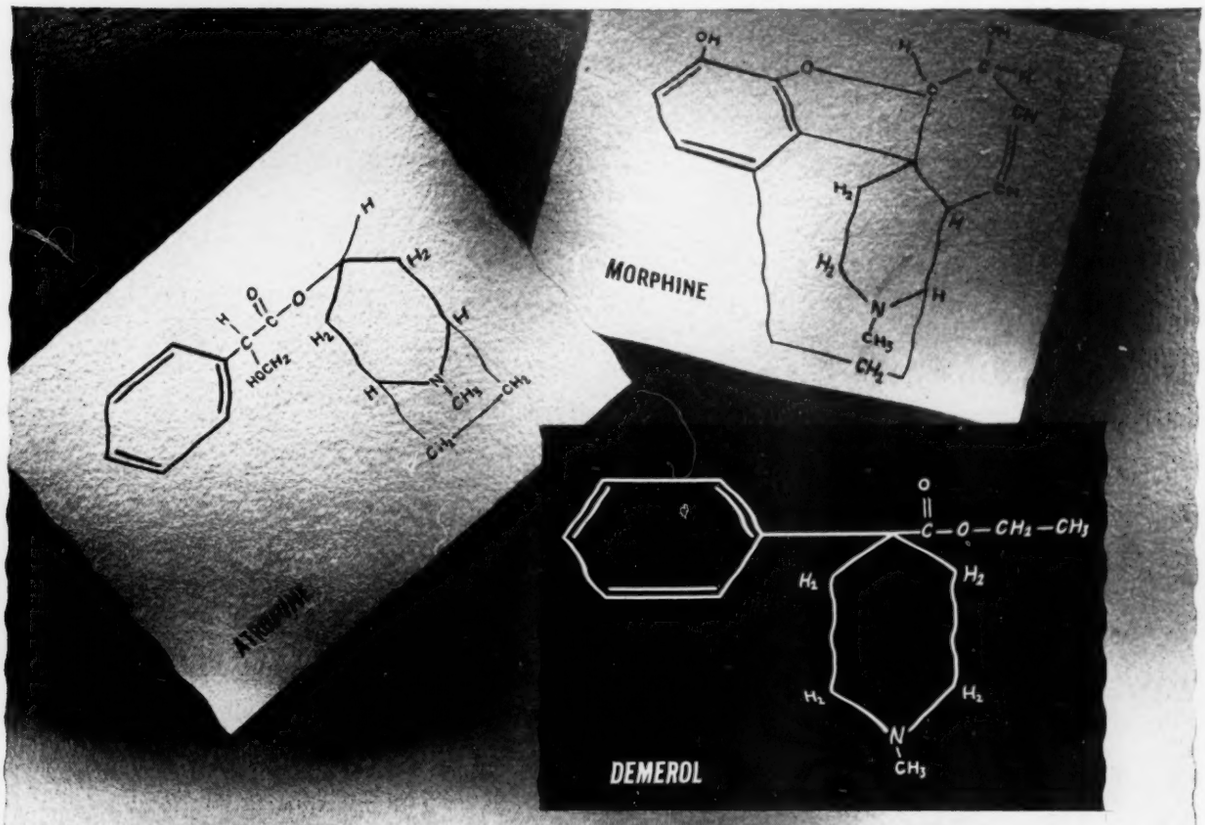


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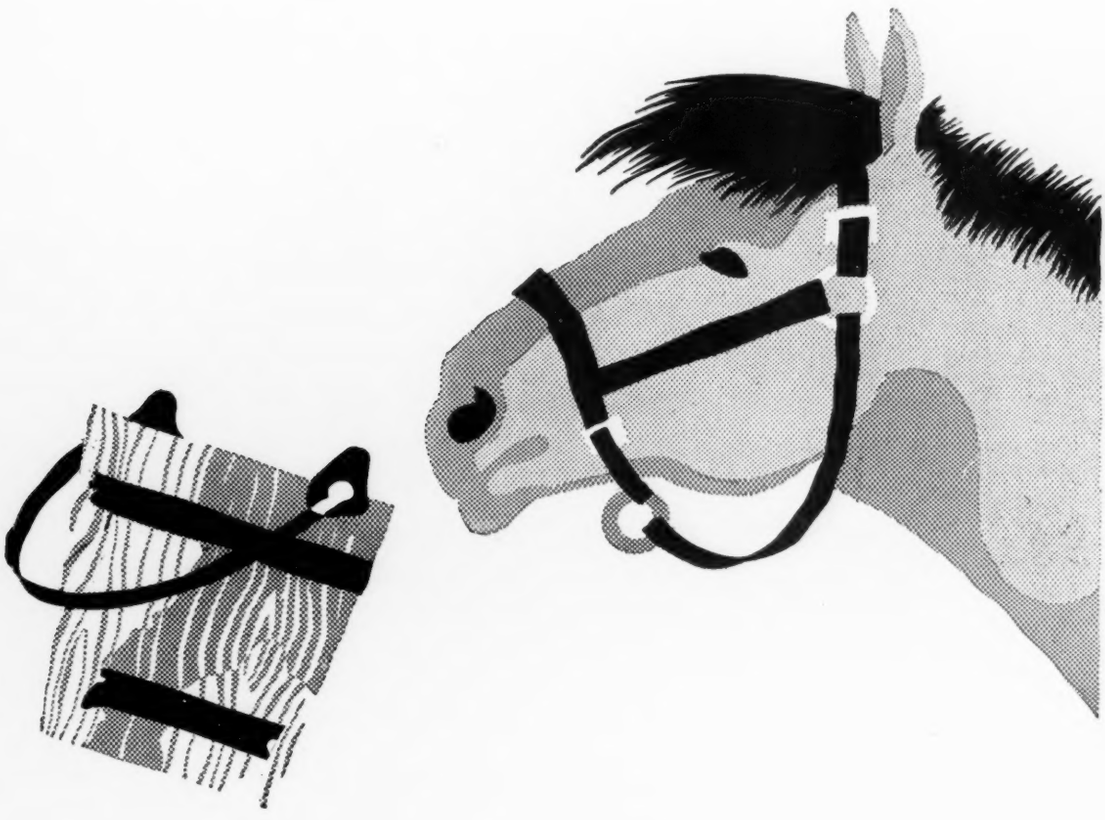

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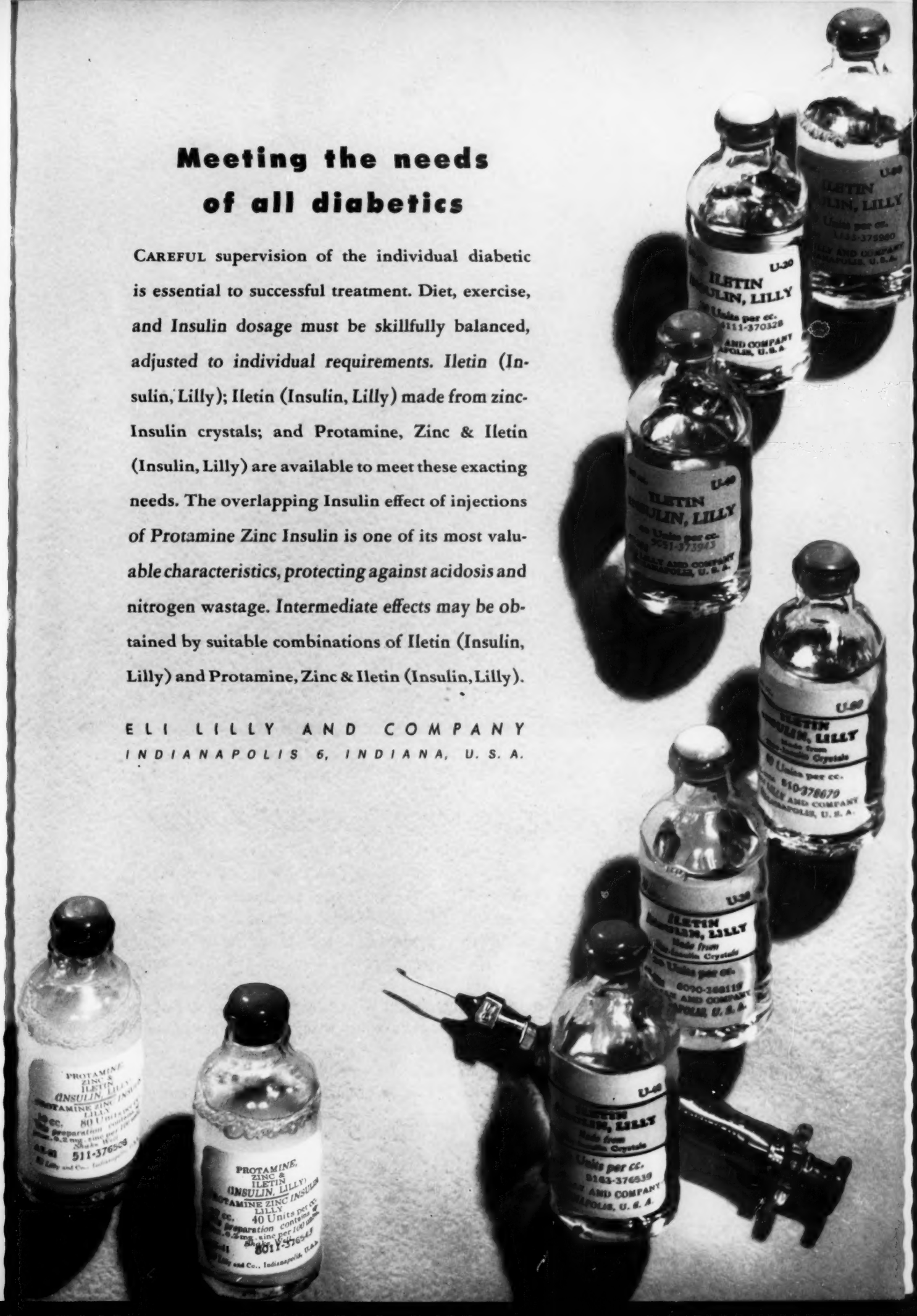

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VOLUME 7 FEBRUARY, 1946 NUMBER 2

# RICHARD HENRY WHITEHEAD

WILLIAM DEB. MACNIDER, M.D.

CHAPEL HILL

President Graham, Dean Berryhill, friends of the University and the Medical School:

It becomes my happy privilege to present to the University on behalf of his admirers this portrait of Richard Henry Whitehead, the first Dean of the Medical School and its first Professor of Anatomy. This excellent likeness of Dean Whitehead was copied by Mr. Alpheus P. Cole from his portrait of Dr. Whitehead at the University of Virginia.

Richard Henry Whitehead received his Bachelor's degree in Arts from Wake Forest College in the spring of 1886. The summer of this year found him devoting hours of each day to the study of anatomy under the guidance of his older brother, Dr. John Whitehead, then an eminent practitioner of medicine in Salisbury, North Carolina. Such was the custom at this and at an earlier period in medical education: to read medicine under a preceptor. In this instance the preceptor was both a learned doctor and a man of superb character.

In the fall of this year young Whitehead entered the Medical Department of the University of Virginia. He completed in one year with distinction the two-year medical curriculum of that University, and received the degree of Doctor of Medicine. During that year he came under the influence and tutelage of Dr. William B. Towles, the Professor of Anatomy, who recognized Whitehead's great ability and offered him the post of Demonstrator of Anatomy. In this capacity he served the University of Virginia from 1887 to 1889. In these years, probably, were sown the seeds of thought and method which were later to ripen into great teaching ability and productive scholarship.

The period of 1889-90 was spent by Dr. Whitehead in study at different hospitals in New York and Philadelphia, in order that he might return to Salisbury in the summer of 1890 to form a partnership with his older brother, John Whitehead, for the practice of medicine. It was the object of this association for the older member to devote himself to general medicine, while Dr. Richard Whitehead was to confine himself as much as possible to the practice of surgery. During the summer of 1890 Dr. Whitehead received the call from the University of North Carolina to revive its Medical School, which had previously been established by Dr. Thomas W. Harris, and to become its first Dean and Professor of Anatomy. One may well imagine the conflicts of purpose which followed this call—whether to remain in Salisbury, where he was assured of the success and financial remuneration which had come to his father, Marcellus Whitehead, and to his brother, John; or to think of students such as he had had at Virginia, of the influence of Towles as guide and teacher, and come to the University of North Carolina to undertake an educational adventure which to date had not been successful.

He accepted the academic challenge with vigor, poise and dignity, and took over his duties at Chapel Hill in the fall of 1890. These duties embraced organizing the Medical School, teaching anatomy, physiology and materia medica (now designated pharmacology), and serving as University physician, physician for the University faculty, to a considerable extent physician for the

Given on the occasion of the presentation of a portrait of Dr. Whitehead to the Medical School of the University of North Carolina, November 25, 1945.

people of Chapel Hill and the surrounding country, and as consultant in medicine for this area of the state. He attended to these duties with a will and an exactness which sought perfection. He found time for the cultivation of flowers, for hunting, and for loving with great tenderness the kindly things of nature.

During these early years in the life of this great teacher and practitioner of medicine, he became aware of the necessity for research as an essential part of the life of a student-teacher. In order to satisfy this desire, Dr. Whitehead studied for several summers at the University of Chicago under the guidance of Dr. Lewellys F. Barker, then Professor of Anatomy at that institution. Between these two scholars there developed great intellectual respect and fine affection. Later, after Professor Barker had returned to the Johns Hopkins Medical School as Professor of Medicine and Physician-in-Chief to the hospital, Dr. Whitehead went to this institution and worked in the laboratory of Dr. F. P. Mall, the Professor of Anatomy.

This course of events, this yearning for greater understanding and for creative scientific work, may appear both natural and easy until we think of the difficulties which must have beset this road of intellectual advancement. Dr. Whitehead had spent only one year in an institution as a student of medicine, and a part of another year in hospitals in preparation for the practice of medicine; then came the determination, not only to teach with excellence at a university level of instruction, but through inquisitiveness as research to contribute to such an order of understanding. Dr. Whitehead very quietly, methodically, and resolutely went forward to accomplish his ideal. He taught himself German, French and Italian, that he might have these tools for his investigations. He sparsely equipped a small laboratory for histological and embryological investigation, and here without assistance he made important contributions in these areas of knowledge.

In this abbreviated statement concerning the life of Dr. Whitehead, both students and teachers may find not only a fine example but a sustaining stimulus in the power of the will of man to know. In the summer of 1905 Dr. Whitehead accepted the Deanship of the School of Medicine at the University of Virginia.

Finally, as we commemorate the accomplishments of Richard Henry Whitehead this afternoon by receiving into our University organization a portrait of the man, I would have you envision a quiet, simple, strong type of splendid gentleman who carried with him that something which partakes of greatness. These qualities, over and above his specific attainments, bound students and colleagues to him with a respect and an affection which lasted for the life of the individual. With the lapse of years these values in the man have lingered in this school, have given to it character and stability of purpose, and have guided its teachers along paths of thoughtfulness and investigation. Through such teachers, students have received sound and exacting instruction.

"Richard Henry Whitehead lived his life and went his way and those about him knew it was a good life and a straight way and worthy of infinite trust."

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# THE PATHOGENESIS OF THE TOXEMIAS OF LATE PREGNANCY

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WINSTON-SALEM

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From the Department of Obstetrics and Gynecology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C. Awarded the B. Bernard Weinstein prize for the best senior obstetrical paper, 1945.

### *Definition of Terms*

In order to discuss intelligently such a broad subject as the toxemias of pregnancy, some limitation must be placed on the definition. The classification of toxemias of pregnancy suggested by the American Committee on Maternal Welfare in 1939[1] is as follows:

**Group A. Disease not peculiar to pregnancy:**
1. Hypertensive or Arterial Vascular Disease
   a. Benign: mild; severe, cardiorenal
   b. Malignant
2. Renal Disease
   a. Glomerulonephritis: acute; chronic (mild or severe)
   b. Pyelonephritis: acute; chronic
   c. Other forms of severe renal disease: Nephrosis, polycystic kidneys, and other congenital anomalies of the kidneys

**Group B. Disease dependent on, or peculiar to, pregnancy:**
1. Mild pre-eclampsia
2. Severe pre-eclampsia (preconvulsive)
3. Eclampsia

**Group C. Vomiting of pregnancy**

**Group D. Unclassified toxemias**
   a. Those patients in whom a definite diagnosis cannot be made to allow them to fall into Group A or B (i.e. glomerulonephritis suspects)
   b. Many will fall into the above-known groups post partum, but insufficient data before or in the early months of pregnancy make it imperative to exclude them from statistical data except when autopsy findings ultimately allow them to be put in either Group A or B.

In this discussion, the term "toxemia of pregnancy" is limited to the cases which fall into Group B in the above classification—"disease dependent on, or peculiar to, pregnancy." Pre-eclampsia occurs during the last half of pregnancy and is most frequently observed in the last trimester. It is characterized by the following symptoms and signs: (1) a rise in blood pressure, (2) albuminuria, (3) a rapid gain in weight, (4) edema, (5) headache, (6) diminished urinary output, (7) visual disturbances, and (8) epigastric pain[2]. Pre-eclampsia is that form of toxemia which ultimately may develop into eclampsia, unless the fetus dies or the pregnancy is terminated, or unless the clinical course is altered by appropriate treatment.

When convulsions occur, the term eclampsia is applied. Beck[2] states: "It seems best to consider all of the so-called toxemias of late pregnancy as a single entity which reaches the acme of its development when convulsions occur, the different types being merely differences in the degree of the same disease."

### *Theories*

Toxemia of pregnancy has been appropriately referred to as the "disease of theories." Critical reviews dealing with the causation of eclampsia are numerous. In one of the earliest such reviews, Berkeley[3] divided the theories into (1) the mechanical or ancient and (2) the modern or toxemic theories. Eclampsia was originally attributed to a mechanical increase of intra-abdominal pressure which somehow increased the arterial tension, or to the pressure of the growing uterus on the renal veins or on the arteries.

Later observers recognized the generalized effect of toxemia and postulated that a toxic product was formed during pregnancy. No one was able to isolate this toxin, however. The poison was thought to arise from the placenta, the fetus, an infectious organism, the intestines, the thyroid, or the kidney. The early German workers regarded eclampsia as an auto-intoxication due to a poison of syncytial origin.

F. J. Browne[4] has reviewed the recent hypotheses, which are based on the following factors:

(1) Role of the internal secretory glands
   a. the pituitary gland
   b. the adrenal glands
   c. the anterior pituitary-like hormone
(2) Dietetic factors
(3) Placental toxin
(4) Pressure
(5) Pyelitis and toxemia
(6) Allergy
(7) Infection
(8) Chemical poisons
(9) Constitutional predisposition
(10) The rhesus factor

A review of the above theories shows none to be based on conclusive evidences.

### *The Concept of Arteriolar Spasm*

A more rational approach to the problem would be to determine whether there is a single underlying pathologic-physiologic process which could account for the varied and seemingly unrelated symptoms and signs observed in a toxemic patient. Irving[5] in 1936 wrote: "Of late years the conviction has grown that eclampsia and its precursor, pre-

1. Stander, H. J.: A New Classification of the Toxemias of Pregnancy, Am. J. Surg. 48:112-117 (April) 1940.
2. Beck, A. C.: Obstetrical Practice, ed. 3, Baltimore, Williams & Wilkins, 1942, chap. 26.
3. Berkeley, Comyns: The Causation of Eclampsia, J. Obst. & Gynaec. Brit. Emp. 5:40-58, 1904.
4. Browne, F. J.: The Aetiology of the Toxaemias of Late Pregnancy, J. Obst. & Gynaec. Brit. Emp. 51:438-471 (Oct.) 1944.
5. Irving, F. C.: The Vascular Aspect of Eclampsia, Am. J. Obst. & Gynec. 31:466-476 (March) 1936.

eclampsia, is not a disease primarily of the liver, or of the kidneys, or indeed of any individual organ, but an affection of all the small terminal arterioles. This concept was first advanced by Volhard in 1918, and has been accepted by Hynemann, Hinselmann, and Fahr."

Beck[2] assumed the presence of some unknown factor which causes a spasm of the arterioles in different parts of the body. This arteriolar spasm deprives the capillary cells of their oxygen supply and thereby increases the permeability of the capillaries. Mussey[6] agreed with Beck. Addis[7] attributed all of the lesions of toxemia to "angiospasm."

### *Pathologic Anatomy*

There is considerable clinical and experimental evidence to show that the theory of arteriolar spasm could explain all of the clinical symptoms and signs of toxemia, as well as the autopsy findings.

#### *Kidney*

As long ago as 1880 Cohnheim suggested that albuminuria and oliguria might result from spasm of the renal arteries. In 1924 Fahr[8] published his classical description of the kidneys in toxemia. He found that the size of the glomeruli was increased by swelling of the capillary walls, and that a relative absence of blood cells in the capillary lumina produced a marked ischemia. Fahr considered these changes in the glomeruli to be due to spasm of the afferent arterioles, and believed that they were accompanied by swelling of the vessel wall. The tubules were described as exhibiting albuminous degeneration.

Bell[9] in 1932, by the use of a special azocarmine stain, demonstrated a massive thickening of the capillary basement membrane. He felt that the essential lesion was an injury to the glomerular capillaries which allowed albumin to escape and which impeded the flow of blood through the kidneys. It was not clear to him whether this injury was inflammatory or degenerative. Bell also described cloudy swelling of the tubules and stated that it was a "typical effect of toxin or toxic substances in the circulating blood, but it may also result from anemia caused by spasm of the renal arteries." Bell favored the toxin theory.

Baird and Dunn[10] described glomerular lesions similar to those reported by Fahr. They stressed the diffuseness of the lesions, which involved every tuft. In the majority of their cases the first convoluted tubules were fairly normal, apart from varying degrees of early autolytic changes which could be interpreted as early cloudy swelling. Necrosis was not noted in any tubule. The authors felt that the above findings did not support the view that there is in eclampsia a protoplasmic poison circulating in the blood. "Such alterations as do appear may arise directly or indirectly as a result of the glomerular lesion." It seems reasonable to suppose that, with afferent arteriolar spasm, diffuse tubular degeneration will occur.

Baird and Dunn[10] regarded the eclamptic lesions as closely similar to those of glomerulonephritis, and differing only in degree and not in kind. Addis[7] stated that the renal lesions of eclampsia are similar morphologically to those of acute glomerulonephritis. Baird and Dunn agreed with Fahr[8] and Bell[9] that a glomerular lesion is always present in eclampsia and that it tends to diminish the freedom of circulation through the glomeruli. They considered the glomerular lesion to be a response to some stimulus. They also concluded that the glomerular changes are not due to a rise in blood pressure and that the glomerular obstruction is not the cause of the hypertension of toxemia.

Infrequently, a symmetrical cortical necrosis is found in the kidneys of a patient dying of eclampsia. Bell[9] describes almost complete necrosis of the cortices of both kidneys, with thrombosis of the interlobular arteries and usually of the vasa afferentia also. Sometimes thrombi are found in the glomerular capillaries. The larger branches of the renal arteries are free of thrombi. Bell considered the thromboses as the primary condition, and the necrosis as secondary to the infarction. Baird and Dunn[10] believed that vascular spasm occurs first, and that thrombosis develops when the blood flow is reestablished after the spasm has ceased. Duff and Murray[11] agreed with Bell's conclusions.

6. Mussey, Robert D.: The Relation of Retinal Changes to Severity of Acute Toxic Hypertensive Syndrome of Pregnancy, Am. J. Obst. & Gynec. 31:938-946 (June) 1936.
7. Addis, W. R.: Pathogenesis of Eclampsia, Brit. M. J. 1: 1103-6 (May 29) 1937.
8. Fahr, K. T., cited by Hinselmann(15).
9. Bell, E. T.: Renal Lesions in the Toxemias of Pregnancy, Am. J. Path. 8:1-42 (Jan.) 1932.
10. Baird, D., and Dunn, J. S.: Renal Lesions in Eclampsia and Nephritis of Pregnancy, J. Path. & Bact. 37:291-301 (Sept.) 1933.
11. Duff, G. L. and Murray, E. G. D.: Bilateral Cortical Necrosis of Kidneys, Am. J. M. Sc. 201:428-450 (March) 1941.

*Liver*

According to Irving[5], Schmorl first described the liver changes of eclampsia in 1883. The characteristic lesions were found at the periphery of the lobule and consisted of fibrin thrombi in the capillaries, with hemorrhage and necrosis of the adjacent liver cells. Acosta-Sison[12] in 1931 studied 38 cases at autopsy and reported that death from eclampsia may occur without demonstrable pathologic lesions in the liver, kidneys, heart, or brain which are extensive enough to justify the severity of the symptoms. He noted areas of hemorrhage, necrosis and fatty degeneration in the liver, usually predominant at the periphery of the lobules, but also found in the central and mid-zonal portions. He felt that the lesions in the various organs had a common origin, "presumably a toxin or an altered blood condition."

Irving[5] also noted hemorrhage, necrosis, and fatty degeneration in the lobules. Because he found thromboses in the radicles of the portal vein or in the small branches of the hepatic artery occupying the portal spaces, he concluded that the liver lesions could be on a vascular basis. Bell[9] stated that thrombosis of the small vessels seems sufficient to account for the areas of necrosis and hemorrhage, but that the diffuse injury of the hepatic cells is best explained as the effect of a circulating toxic substance.

Addis[7] stated that there is as much reason to believe that the liver lesions are due to arteriolar spasm with capillary ischemia as there is to consider the renal lesions as due to this cause. According to this investigator, the essential lesion in eclampsia is periportal hemorrhagic necrosis. The hepatic artery contributes one-fourth of the blood supply to the lobule and 40 per cent of the oxygen; the main central portion is oxygenated by the portal veins. The liver lesions have all the characteristics of severe multiple infarctions and are confined to areas supplied by the hepatic arteries—the only areas where angiospasm could cause ischemia. Addis felt that if the eclamptic lesions were due to cell injury by some toxic substance circulating in the blood, it would be difficult, in view of the open nature of the sinusoids into which the capillaries open, to understand the strict localization of the lesion in the periportal areas at the periphery of the lobule.

*Adrenals and Spleen*

The adrenals and spleen are also reported as showing vascular lesions—hemorrhages, which may very well be explained on the basis of arteriolar spasm.

*Brain*

The brain lesions of eclampsia, as they were first decribed by Braunmeuhl, consisted of ischemic cell disease believed to be due to vasoconstriction. Jaffe in 1927 thought that vascular spasm may cause necrosis of the vessel wall, followed, on relief of the constriction, by vascular rupture due to the sudden access of blood. Benoit and DeVries attributed the brain changes to primary spasm of the cerebral arteries and arterioles.

Beck[2] stated that the only gross lesion found at autopsy is anemia of the cortex. Often edema is present, and multiple minute hemorrhages are common. Microscopic examination showed hemorrhage associated with small foci of softening in which the arteries revealed evidences of degeneration. The fact that the area of parenchymal damage was found to extend beyond the area supplied by the injured vessels indicated that the ischemia was greater than could have been produced merely by the vascular changes noted. This observation led to the assumption that the primary disturbance is an arteriolar spasm which is somewhat more extensive than is the final vessel lesion. When the circulation is restored, red cells escape and thrombosis occurs as a result of the changes in the endothelium.

*Lung*

The lungs of eclamptic patients at autopsy reveal congestion and edema, together with petechial hemorrhages in some cases. Addis[7] stated that ischemic injury to the alveolar capillaries by intermittent spasm of the pulmonary arterioles would be expected to result in edema and congestion.

### *The Pathologic Physiology*

*Kidney*

Welsh, Wellen, and Taylor[13] measured the rate of glomerular filtration (inulin clearance) and the effective renal blood flow

12. Acosta-Sison, H.: A Clinicopathologic Study of Eclampsia Based upon 38 Autopsied Cases, Am. J. Obst. & Gynec. *22:35-43 (July) 1931.*

13. Welsh, C. A., Wellen, I., Taylor, H. C., Jr., and Rosenthal, A.: Filtration Rate, Effective Renal Blood Flow, *Tubular Excretory Mass and Phenol Red Clearance* in Normal Pregnancy, J. Clin. Investigation 21:57-61 (Jan.) 1942.

(diodrast clearance) in normal and toxemic pregnancy. In the normal pregnancy, glomerular filtration and effective renal blood flow were unaffected. In 13 patients with true pre-eclamptic toxemia and in 2 eclamptic patients they found the glomerular filtration rate to be somewhat reduced, as compared with postpartum values. In their opinion, this finding could be due to spasm of the afferent glomerular arterioles or to thickening of the basement membranes of the glomerular capillaries, with increased resistance to the filtration. As a rise in the filtration rate occurred soon after delivery, however, it was thought to be due to arteriolar spasm. The effective renal blood flow in toxemia was found to be normal or even above normal. This finding showed that renal ischemia could not be an essential factor in causing the hypertension of pre-eclamptic toxemia.

The above work may be interpreted as showing that the clinical findings of albuminuria, oliguria, hematuria, and tubular casts can be caused by arteriolar spasm. Vascular spasm of the afferent vessels produces anoxemia of the walls of the glomerular loops, which become more permeable, allowing albumin to pass through. The sudden onset of marked albuminuria which so often precedes or accompanies an eclamptic attack may be satisfactorily explained on the basis of an abrupt arteriolar spasm. With the relief of the attack the albumin disappears rapidly.

To support this view is the experimental work of Chesley, Markowitz, and Wetchler[14], who produced albuminuria in pregnant women by immersing the hand in ice water. Albuminuria invariably occurred if the systolic and diastolic pressures both rose more than 16 mm. of mercury. They concluded that the onset of albuminuria coincided with the release of vascular spasm. The spasm causes anoxia which, if continued more than three minutes, damages the capillary wall and renders the glomeruli permeable to protein.

The oliguria may also be explained on the basis of arteriolar spasm; the more extensive the spasm, the less the amount of blood which passes through the glomeruli. In the absence of sufficient fluid to hold it in solution, the albuminous material solidifies and forms casts in the tubules.

The hematuria results from stagnation of blood in branches of the afferent arterioles, which supply the tubules. These arterioles may rupture into the tubules. Another possible cause is bleeding into Bowman's capsule when the spasm of the afferent arterioles is released.

*Peripheral circulation*

(1) *Capillary studies*

The peripheral circulation in pre-eclamptic and eclamptic patients shows evidences of arteriolar spasm. By means of the capillary microscope Hinselmann[15] in 1924 observed the behavior of the capillaries at the base of the nails in toxemic patients. He saw constantly recurring spasmodic contractions of the capillaries. Thickening of the venous loop, stasis, and granular flow were described. Occasionally vascular spasm caused the disappearance of an arterial loop, followed by a like disappearance of the venous loop as if from the action of a peristaltic wave.

(2) *Retinal changes*

Many observers have noted changes in the arterioles in the fundus oculi. At first localized spastic constrictions of the retinal arterioles are seen. One artery may be affected more than another, and the irregularities in the calibre of the vessels change in position every few minutes. Later, the constrictions cease to shift, and become more marked. Following this development, a suggestion of edema is observed in the immediate vicinity of the vessels[2]. Hemorrhagic areas and cotton-wool exudate follow. Finally, diffuse albuminuric retinitis results. Wagener[16] noted that the changes in the arterioles may disappear entirely if there is an early and permanent fall in the blood pressure. He believed that this spastic process might pass into a permanent sclerosis if the pre-eclamptic state were allowed to continue.

Masters[17] in the routine ophthalmoscopic study of pregnant women, found that every patient whose systolic blood pressure was elevated to 150 mm. or more showed narrowing of the calibre of the retinal arteries. This narrowing was also seen in every one of 44 toxemic patients, and was observed in 3 pa-

14. Chesley, L. C., Markowitz, I., and Wetchler, B. B.: Proteinuria Following Momentary Vascular Constriction, J. Clin. Investigation 18:51-58 (Jan.) 1939.

15. Hinselmann, H.: Die Eklampsie, Bonn, 1924, p. 361.
16. Wagener, H. P.: Arterioles of Retina in Toxemia of Pregnancy, J.A.M.A. 101:1880-4 (Oct. 28) 1933.
17. Masters, R. J.: Routine Ophthalmoscopic Examination as Aid in Management of Maternity Cases, Tr. Am. Ophth. Soc. 31:416-450, 1933.

tients whose systolic pressure was initially less than 150 mm., but subsequently rose much higher.

Mussey[6] made ophthalmoscopic examinations in 98 cases of pre-eclampsia and 10 cases of eclampsia. The systolic blood pressure was 140 mm. or more in all the cases. He stated that there is some evidence that the diastolic pressure is elevated out of proportion to the systolic pressure in the more severe degrees of toxemia. Seventy-two per cent of the 108 patients he examined showed some changes in the retinal arterioles and in the retina proper. The severity of the changes in the retinal arterioles appeared to be in direct proportion to the height of the systolic pressure and to the duration of the hypertension. Mussey agreed with Wagener that the variability of the arteriolar narrowings and their usual tendency to disappear after the termination of toxemia suggest that they are visible signs of a functional or angiospastic lesion rather than of arteriosclerosis. When the vascular lesion in the retina is marked and severe, it may be assumed that similar lesions are present in the arterioles elsewhere.

(3) *Vascular changes in the muscles*

In a small number of patients with pre-eclamptic toxemia on the obstetrical service at the Mayo Clinic, small sections of muscles were obtained at or about the time of delivery[6]. These sections disclosed alterations in the arterioles identical with those seen by Keith, Barker and Kernohan[18] in biopsy specimens from the pectoral muscles of non-pregnant patients with vascular disease and glomerulonephritis.

*Hypertension*

The hypertension of toxemia cannot be regarded as the result of obstruction to the renal circulation, since the effective renal blood flow in toxemia has been found to be normal or even above normal. Since 1934 our concept of the etiology of hypertension in general has been dominated by the experimental work of Goldblatt and his coworkers, who first produced persistent experimental hypertension in animals by partially constricting one or both renal arteries to cause renal ischemia. The experimental hypertension produced by clamping one kidney can be cured by the removal of the damaged kidney. This mechanism of producing hypertension has been found to be independent of nervous control and has been thought to be on a humoral basis. The cortex of an ischemic kidney produces renin, which is not directly a pressor substance, but which combines with an activator in the blood to produce angiotonin (hypertensin). Angiotonin has been isolated. When injected into human subjects, it reduces the effective renal blood flow, apparently by causing constriction of the efferent glomerular arterioles. The effect is exactly the opposite of that produced in pre-eclamptic toxemia. It is therefore evident that the hypertension of pre-eclamptic toxemia cannot be due to a renin-hypertensin mechanism like that at work in the Goldblatt experiment, or to a primary renal ischemia from any cause whatsoever. Browne[4] concluded that, although the cause of the hypertension of pre-eclamptic toxemia is not exactly known, we can say with certainty: (1) that it is due to a humoral and not to a nervous mechanism; (2) that it is not due to renal ischemia, nor to angiotonin, tyramine, or adrenaline; and (3) that during her pregnancy, and probably after the third month, the woman who develops pre-eclamptic toxemia acquires a sensitivity to the action of certain pressor substances; and (4) that this sensitivity does not seem to be due to any constitutional predisposition.

Byrom[19] produced transient somatic vasoconstriction in female albino rats by the subcutaneous injection of vasopressin (Pitressin, Parke-Davis) twice daily over a period of days. The renal lesions produced closely resembled those found in pre-eclamptic toxemia and in eclampsia. Byrom concluded that: "vasopressin is therefore capable of producing a morbid state resembling in many respects pre-eclampsia and eclampsia, and the discrepancies mentioned would perhaps disappear if a continuous absorption of vasopressin could be ensured." The findings were felt to strengthen the view that many of the clinical and anatomic features of toxemia could be expressions of vascular spasm.

Irving[5] found that the blood pressure in toxemic patients is extremely variable, and that when the blood pressure is taken in both arms simultaneously the readings not infrequently differ as much as 20 mm. This

18. Keith, N. M., Barker, N. W., and Kernohan, J. W.: Histologic Study of Arterioles in Various Types of Hypertension, Tr. A. Am. Phy. 46:66-70, 1931.

19. Byrom, F. B.: Morbid Effects of Vasopressin on Organs and Vessels of Rats, J. Path. & Bact. 45:1-16 (July) 1937.

phenomenon strongly suggests vascular spasm affecting different vessels unequally.

The physiologic factors which determine blood pressure are: (1) output of the heart, (2) the force of cardiac contraction, (3) the viscosity of the blood, and (4) the peripheral resistance. There is no evidence that the first three factors are altered in pre-eclamptic toxemia sufficiently to cause clinical manifestations. Therefore, the hypertension may be attributed to an increase in peripheral resistance.

Beck[2] stated that after delivery of the child the blood pressure falls almost as rapidly as it rose and, in 75 per cent of all eclamptic patients, is normal by the tenth postpartum day. Irving[5], however, stated that the usual sequel of pre-eclampsia or eclampsia is permanent vascular hypertension, probably due to thickening of the arteriolar walls. Corwin and Herrick[20], in a study of 165 patients with hypertensive toxemias of pregnancy, found that 74 per cent showed cardiac hypertrophy, sclerosis of the radial and brachial arteries, and vascular eye changes for six months to six years post partum, and that one third of these patients exhibited persistent hypertension. Welsh, Wellen and Taylor[13] noted that there was no constriction of the efferent glomerular arterioles in pre-eclamptic toxemia during pregnancy, but that it appeared after delivery if the patient developed chronic hypertension.

Peckham's observations[21] may explain the discrepancies in the statistics quoted above. He noted that the incidence of chronic nephritis following pre-eclamptic toxemia was influenced directly by the height of the blood pressure and the duration of the toxemia. Chronic nephritis did not develop in patients whose systolic blood pressure remained less than 170 mm. during acute toxemia. Fifteen per cent of the patients with pressures between 170 and 200 mm. and 48 per cent of the patients whose blood pressure was over 200 mm. developed chronic nephritis.

*Edema*

Physiologists long have known that the permeability of the vessel walls may be increased by an impairment of their oxygen supply, with resultant edema. Such an anoxemia may be caused by arteriolar spasm. The capillaries are normally permeable to water and dissolved salts, but not to proteins. If through any injury the capillaries become abnormally permeable, they will allow the passage of proteins in greater or lesser degree. The tissues containing the protein then acquire an osmotic pressure of their own, and the tendency to the passage of water from the veins into the tissues is increased. The resultant edema may cause a rapid increase in body weight.

In acute glomerulonephritis the protein content of the edema fluid is greater than that of blood—a finding suggestive of damage to the capillary walls. There are very few studies on the protein content of the edema fluid in toxemia. Hellmuth[22] in 1922 obtained edema fluid by puncture from 29 patients with eclamptic or pre-eclamptic toxemia. He found the protein content to be low—less than 0.14 per cent in 26 of the patients. In the other 3 it varied from 0.25 to 0.35 per cent. On the basis of these findings it was assumed that capillary permeability is not increased even in the most severe cases.

Whether general capillary permeability is increased with the onset of albuminuria is not known with certainty. If the greater permeability of the glomerular capillaries presumed to be responsible for albuminuria is due to arteriolar spasm, this increase in capillary permeability would probably be general throughout the body and might increase the edema already present. It is probable, however, that at least some of Hellmuth's patients had albuminuria. The fact that the protein content was low in spite of this fact might be thought to cast doubt on the accuracy of Hellmuth's figures.

*Hypertensive encephalopathy*

The pathological changes found at autopsy in the brain of an eclamptic patient have been previously described. The essential feature in eclampsia is an arterial hypertension which rises rapidly just before the onset of the seizure, or coincident with it. The attack starts with general tonic spasm, which gives way to clonic convulsions, followed by coma. The pupils are dilated and react sluggishly. Babinski's sign is positive. The cerebrospinal fluid pressure is raised.

20. Corwin, J. and Herrick, W. W.: Toxemias of Pregnancy in Relation to Chronic Cardiovascular and Renal Disease, Am. J. Obst. & Gynec. 14:783-796 (Dec.) 1927.
21. Peckham, C. H.: Chronic Nephritis Following Eclampsia, Bull. Johns Hopkins Hosp. 45:176-188 (Sept.) 1929.
22. Hellmuth, K.: Refractometric Determination of Albumin in Edema Fluid in Kidney Affections of Pregnancy and in Eclampsia, Zentralbl. F. Gynaek. 46:290-296 (Feb. 25) 1922.

Hypertensive encephalopathy is found in three conditions: (1) eclampsia, (2) lead poisoning, and (3) acute glomerulonephritis. Vaquez in 1904 showed that the colic of lead poisoning was due to constriction of the mesenteric vessels. Addis suggested that the same mechanism might be the cause of the epigastric pain in toxemias. The arteriolosclerosis of chronic lead poisoning is thought to result from spasm of the media. Postmortem examinations in all three of the above conditions show the brain to be pale and bloodless. Edema due to capillary ischemia is often present. These findings, together with the sudden onset and short duration of the attacks, are very suggestive of intracranial angiospasm. This would be the simplest explanation of the cerebral ischemia. The presence of Babinski's sign, which is absent in the irritative seizures of uremia, indicates that cortical control is cut off by ischemia. It would be difficult to explain the positive Babinski reaction by any other mechanism in such a condition as eclampsia.

A rise in temperature occurs in the severely toxemic patients. Addis states that only a very severe angiospasm will suffice to affect the heat-regulating center in the corpus striatum. It is not surprising that the prognosis in such a case is grave.

### *Physiological Factors in the Production of Arteriolar Spasm*

The physiological factors which control the tone of blood vessels are: (1) the balance between the sympathetic and parasympathetic nervous systems, (2) local nervous axon "reflexes," (3) local temperature changes, and (4) chemical agents—hormonal or metabolic[23].

Constriction and dilatation of the blood vessels are controlled by the vasomotor center situated on the floor of the fourth ventricle at the level of the calamus scriptorius. No substance has been identified in eclampsia which would stimulate the vasoconstrictor fibers. That local axon reflexes are not entirely responsible for the arteriolar spasm is shown by the diffuseness of the process. Local temperature changes cannot explain all of the findings.

It has been found that arteriolar spasm can be produced by the direct action of pituitary extract upon the vessel walls. Anselmino and Hoffman[24] prepared an ultrafiltrate from the blood of eclamptic and preeclamptic women and injected it into rabbits with known diuresis curves. They found that the injection of such ultrafiltrates would cause anuria, retention of chlorides, and an elevation of blood pressure. An ultrafiltrate prepared in the same manner from the blood of normal pregnant women did not have this effect. Similar results were obtained by the injection of pituitary extract. Anselmino and Hoffman stated that their ultrafiltrate resembled pituitary extract in that it was rendered inert by exposure to ultraviolet light and alkalinization, and was absorbed by talcum. They reasoned that the toxic agent in eclampsia might be pituitary extract. Unfortunately, their findings have not been confirmed by other investigators. Hurwitz and Bullock[25] repeated the experiments with entirely negative results.

Byrom[19], from his experiments with vasopressin, concluded that it would be dangerous to assume that the spasm produced in toxemia is necessarily due to an oversecretion of vasopressin, although he found that pregnant rats seemed to be somewhat hypersensitive to vasopressin. He concluded: "If the hypothesis of vascular spasm is accepted, then either some unknown pressor agent is concerned, or alternatively the vessels must become in some way hypersensitive."

The other chemical cause of alteration of vascular tone may be some metabolic product. Kapeller-Adler[26] studied the histidine-histamine relationship in normal and toxemic pregnancies. Histidine is a constituent of the urine throughout normal human pregnancy, the excreted amounts ranging between 15 and 50 mg. per 100 cc. Kapeller-Adler found histidine excretion considerably decreased in patients with severe preeclamptic toxemia. In some cases none or only a trace was found. So constant were these findings that a marked diminution in histidine excretion was suggested as a diagnostic sign of severe toxemia of pregnancy.

Kapeller-Adler[27] also found that, concom-

23. Bard, P.: MacLeod's Physiology in Modern Medicine, ed. 9, St. Louis, C. V. Mosby, 1941.

24. Anselmino, K. J. and Hoffman, F.: Die Uebereinstimmungen in den klinischen Symptomen der Nephropathie und Eklampsie der Schwangeren mit den Wirkungen des Hypophysenhinterlappenhormons, Arch. f. Gynaek. 147:597-603, 1931.

25. Hurwitz, D., and Bullock, L. T.: Failure to Find Pressor and Antidiuretic Substances in Patients with Toxemia of Pregnancy, Am. J. M. Sc. 189:613-619 (May) 1935.

26. Kapeller-Adler, R.: Histidine Metabolism in Normal and Toxemic Pregnancy, J. Obst. & Gynaec. Brit. Emp. 48: 141-154 (April) 1941.

27. Kapeller-Adler, R.: Significance of Isolation of Histamine from Urine in Toxaemia of Pregnancy, Ibid, 155-160.

itant with the low histidine excretion, there was a high excretory value for histamine. In patients with normal histidine excretion, a detectable quantity of histamine could not be obtained from the urine. She felt it probable that in severe toxemia histidine, instead of being excreted, was transformed into histamine. When the chemical structure of histidine is considered, the possibility of a transformation of this inactive substance into the active histamine becomes obvious.

According to Kapeller-Adler, "There is no doubt that the histamine isolated from urine in cases of the toxemias of pregnancy can have only been derived from histidine, which is normally present in large amounts throughout pregnancy." The activity of two enzymes seems responsible for the rapid formation of histamine in the metabolism of histidine: (1) histidine decarboxylase and (2) histaminase. Animal tissues, particularly the kidneys, contain both enzymes. Whereas histidine decarboxylase, which can alter histidine to histamine, appears to be more effective in an atmosphere lacking oxygen, histaminase, an enzyme tending to destroy histamine, works only if oxygen is present. It has been suggested that the occurrence of histamine in the urine of pregnant women may be determined by the balance between the activity of histidine decarboxylase and that of histaminase. Kapeller-Adler suggested that very small amounts of histamine may be formed in normal pregnancy, and that the less pronounced symptoms such as headache, morning sickness, and dyspepsia which occur in nearly all normal pregnancies may indicate slight intoxication by histamine. She pointed out the similarity between the clinical symptoms of histamine intoxication and those of toxemia of pregnancy. Large doses of histamine cause an intolerable headache, vomiting, unconsciousness, cyanosis, difficulty in breathing, convulsions, and edema.

The pathologic changes produced in the organs of the body by histamine intoxication "so closely resemble those in toxemia of pregnancy that some authors conceived of histamine as the causative factor of eclampsia for that reason alone."[27] Kapeller-Adler suggested that the hypertension of severe pre-eclamptic toxemia may be due to a renal disturbance caused by histamine resulting in a compensatory rise in blood pressure to maintain adequate filtration pressure in the glomeruli. She concluded that the different manifestations of the histamine intoxication may finally depend on the pregnant woman herself, on her adaptability to the changed conditions, and on her state of nutrition. "The sensitiveness of the pregnant woman towards histamine may vary with the individual."[27]

### *Allergy as a Factor in Toxemia*

It is possible that the generalized arteriolar spasm upsets the histidine-histamine balance, leading to excess histamine formation, and to consequent intoxication. However, the initial cause of the arteriolar spasm remains unidentified. Throughout this discussion an altered reactivity or hypersensitiveness of the pregnant woman has been suggested many times. The evidences for the possible role of hypersensitivity in the production of the toxemias of pregnancy follow.

#### *Comparison of acute glomerulonephritis and toxemia*

Addis[7] compared acute glomerulonephritis to eclampsia, and found many resemblances in symptoms and morphological changes. Both diseases are characterized by albuminuria and oliguria, with a high specific gravity, and absence of urinary constituents in the blood. He stated: "The morphological changes in the kidneys in the two diseases differ only in degree rather than in kind." Baird and Dunn agreed with Addis and stated: "We regard the eclamptic lesion as closely similar in nature to that of glomerulitis. Although a distinction can usually easily be made between the two conditions, the difference seems to be one of degree more than of kind."

Addis noted that both acute glomerulonephritis and toxemia are hypertensive conditions and that hypertensive encephalopathy is apt to occur in both. Both are characterized by edema. The liver lesion in one and its absence in the other may depend on a difference in the etiology rather than in pathogenesis.

There are two main theories as to the pathogenesis of acute glomerulonephritis:

The first is credited by Fishberg to Cohnheim and Lichtheim (1877), and is based on the fact that the disease occurs in the course of acute infections, especially scarlet fever and tonsillitis. It describes the condi-

tion as one of generalized toxic injury to the capillaries, of which the kidney lesion is only one manifestation. Addis[7] felt that this concept of a generalized condition is supported by the fact that edema appears early, simultaneously with the appearance of albuminuria or even before it, and by the high protein content of the anasarca fluid. His argument against this theory was that injection into experimental animals of the toxin or endotoxin of Streptococcus scarlatinae, although it did cause an inflammatory reaction, failed to produce the ischemia of the tuft characteristic of acute glomerulonephritis.

The second theory, introduced by Volhard in 1923, suggested that acute glomerulonephritis is the result of a generalized angiospasm producing capillary ischemia. The endothelium of the capillary, accustomed to a pressure of 120 mm. of mercury, might reasonably be supposed to be highly susceptible to anoxemia, which would probably produce an albuminoid degeneration with the formation of small protein molecules. Swelling and increased permeability would then result. The oliguria may be caused by a decreased flow of blood through the tuft or by a fall in intracapillary pressure. Opponents of Volhard's theory ascribed the oliguria to impermeability of the tuft resulting from inflammatory swelling. Addis, however, found that the lumina of the capillaries showed a fixed patency and contained few red blood cells. Volhard showed that the kidney can be perfused after death has relieved the arteriolar spasm.

In the light of our present knowledge, the two theories do not seem to be conflicting. There is sufficient evidence to show that generalized arteriolospasm does occur in acute glomerulonephritis, and that this arteriolospasm can very well explain all the signs and symptoms of the disease. Evidence for the role of arteriolospasm in the pathogenesis of toxemia has already been presented.

Loeb's finding[28] that the blood pressure may fluctuate widely from day to day in acute nephritis suggests that arteriolar spasm is probably the chief underlying mechanism involved. He felt that the cerebral manifestations were not dependent upon nitrogen retention, but were due in part to cerebral ischemia associated with arteriolar spasm and hypertension, and with a greater or less degree of cerebral edema.

The development of edema in glomerulonephritis is due to at least three factors:

(1) A decrease in urine formation resulting from a diminished blood flow through the ischemic glomeruli.

(2) Increased capillary permeability resulting from generalized capillary damage, which allows the abnormal escape of fluid rich in protein to the interstitial spaces.

(3) Elevation of the hydrostatic pressure by congestive heart failure.

The decrease in urine volume is attributed to arteriolar spasm, along with the other two factors mentioned in the causation of edema. The observation that the termination of anuria and the appearance of diuresis may occur too suddenly to be explained by the subsidence of inflammatory lesions lends support to this view.

That acute glomerulonephritis follows infection is generally recognized. Longcope[29] stated that acute hemorrhagic glomerulonephritis may follow tonsillitis, erysipelas, or wound infections, and that it is especially apt to complicate streptococcal infections. In his series of 55 cases of nephritis, 86.3 per cent were preceded by infections. In 31 of the 48 cases with infections the infecting organism was the beta hemolytic streptococcus. There was no evidence to show that the diffuse glomerulonephritis was caused either by lodgment of the streptococci in the glomerular capillaries or by the direct action of bacteria on the kidney.

Hayman and Martin[30] reviewed 77 cases of acute nephritis, and found that 75 per cent followed infection of the upper respiratory tract. There were evidences of cardiac involvement in approximately one half of the cases studied adequately. They noted the frequency with which apparently mild infections of the upper respiratory tract occurred as precursors of the acute nephritis.

Von Pirquet[31] first drew an analogy between the specific complications of scarlet fever, such as acute nephritis, and the occurrence of serum disease one to two weeks after the therapeutic administration of horse serum. He suggested that post-scarlatinal nephritis might be explained as a manifesta-

28. Loeb, R. F.: Nephritis, in Cecil, R. L.: Textbook of Medicine, ed. 6, Philadelphia, W. B. Saunders, 1943, p. 908.

29. Longcope, W. T.: Pathogenesis of Glomerular Nephritis, *Bull. Johns Hopkins Hosp.* 45:335-360 (Dec.) 1929.

30. Hayman, J. M., Jr., and Martin, J. W., Jr., Acute Nephritis; Review of 77 Cases, Am. J. M. Sc. 200:505-514 (Oct.) 1940.

31. Von Pirquet, C. E.: Allergy, Arch. Int. Med. 7:259; 383, 1911.

tion of heightened susceptibility to infection.

At present, the occurrence of glomerulonephritis following infection is not thought to result merely from the interaction of the infectious agent or its product with the organism. Another factor—altered reactivity of the tissues of the host—is thought to play an important part in the production of glomerulonephritis.

Holt and McIntosh[32] stated: "Glomerulonephritis is not due to direct bacterial invasion of the kidney. The latent period between the determinant streptococcal infection and the onset of glomerulonephritis suggests that bacterial toxins themselves are not the cause of renal damage, but that sensitivity of some kind to the bacterial products may develop."

Longcope[29] found that filtered broth cultures of hemolytic streptococci recovered from tonsillar and sinus infections in patients with acute and subacute nephritis gave rise to skin reactions similar to the Dick reaction. Unusually intense reactions were obtained in patients with acute and subacute glomerulonephritis.

Skin tests were conducted with many filtrates of streptococci. Some persons reacted to one and not to another. Longcope found that persons with acute tonsillitis showed a slightly increased tendency to give mild skin reactions, but that patients with acute and subacute nephritis showed a very pronounced tendency to give exaggerated reactions. These results in nephritic patients were interpreted as signifying a high degree of allergy towards some substance in the hemolytic streptococci or in products of their growth. The phenomenon was noted to persist throughout the attack of nephritis and even for several years after apparent recovery from acute nephritis. Longcope concluded that, in view of the great frequency of acute streptococcal infections, acute nephritis must be a rare manifestation.

The theories of Cohnheim and Lichtheim and of Volhard may be combined and slightly altered to form the present theory of acute glomerulonephritis: Following a mild infection, there results, after a certain latent period, an increased susceptibility of the tissues of the host, presumably to the invading micro-organism or to its products or to both. This increased susceptibility causes generalized arteriolospasm, which gives rise to the clinical symptoms and signs of glomerulonephritis.

*Anaphylaxis*

The question which remains to be answered is whether or not altered reactivity plays a role in the pathogenesis of the toxemias of pregnancy.

Rich[33] described the development of hypersensitivity as follows:

"When a foreign protein, whether bacterial or non-bacterial in origin, enters the tissues by whatever route, there ordinarily occurs in the body certain alterations which affect the reactivity of the tissues toward subsequent contact with the protein. When these alterations have occurred, the body is said to have become 'hypersensitive' to the foreign protein, for the tissues will then be readily injured by amounts of the protein that are entirely harmless to the normal body . . . These proteins may be quite harmless to the normal body, but when the state of hypersensitivity has been established as a result of infection (or by the experimental introduction of foreign protein into the body), minute amounts of the proteins will cause local damage and death of tisssues, accompanied by acute inflammation."

Rich differentiated clinically and pathologically between bacterial hypersensitivity and hypersensitivity of the anaphylactic or Arthus type. The anaphylactic type of hypersensitivity is caused by contact of the tissues with a free foreign protein, while protein hypersensitivity results from contact of the tissues with micro-organisms. The anaphylactic type of hypersensitivity is characterized by: (1) rapid reaction to test injection, (2) spasmodic contraction of smooth muscles on contact with the specific protein, and (3) the presence of the sensitizing antibody in the blood stream of the hypersensitive body. Vascular damage is a prominent feature of the histologic picture of the Arthus reaction. Opie[34] described vascular damage and thromboses at the site of reaction. Abell and Schenck[35] observed the vascular changes in the blood vessels of rabbits during the reaction of anaphylaxis. They noted that the injection of antigen into previously sensitized rabbits caused both a marked contraction of the arterioles, which in some instances would completely obliterate the lumina, and a marked stickiness of the leukocytes, which caused clumps

32. Holt, E. L., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, Appleton-Century, 1940, p. 825.

33. Rich, A. R.: Significance of Hypersensitivity in Infections, Physiol. Rev. 21:70-111 (Jan.) 1941.

34. Opie, E. L.: Pathogenesis of Specific Inflammatory Reaction of Immunized Animals (Arthus Phenomenon), J. Immunol. 9:259-268 (July) 1924.

35. Abell, R. G. and Schenck, H. P.: Microscopic Observations on Behavior of Living Blood Vessels of Rabbit During Reaction of Anaphylaxis, J. Immunol. 34:195-213 (March) 1938.

of cells to adhere to the vascular endothelium. In some instances leukocytic emboli were formed which blocked the circulation in the capillaries and veins. The prominence of these vascular changes has suggested that the resulting interference with nutrition is an important factor in producing the tissue damage[36].

Rich[33] stated that there is no doubt that the simple anaphylactic type of hypersensitivity depends upon the presence of antibody. The effective antibody is that portion which is intimately associated with the cells, whether it is actually attached to them or present in the immediately adjacent tissue fluids.

It has been suggested that in the Arthus type of reaction the antigen-antibody union occurs in the arterioles, with resultant arteriolar spasm. This causes vascular damage. The surrounding tissue injury is due to interference with nutrition resulting from the vascular damage and from the clogging of the tissue spaces with hemorrhage and exudate.

Dale and Laidlaw[37] first noted that the pharmacologic effects of histamine were strikingly similar to those seen in anaphylaxis. Dragstedt[38] believed that histamine is the active principle involved in anaphylaxis, and that histamine would explain the smooth muscle stimulation, glandular stimulation, and dilatation of the capillaries. Dragstedt concluded that the cardinal symptoms of anaphylaxis can be explained on the basis of an autointoxication by physiologically active substances which are normally resident in various tissue cells and are liberated from them by some changes in cellular permeability brought about by the antigen-antibody reaction.

*Anaphylaxis in toxemia*

Veit and Weichard were the first to suggest that the entry of placental cells into the mother's circulation could give rise to the formation of antibodies, and that these were the cause of eclampsia.

Rosenau and Anderson[39] were the first North American investigators to suggest that toxemia of pregnancy might be a condition of hypersensitivity. They suggested that "either the blood or proteid substances in solution from the fetus or the placenta may first sensitize the mother. A subsequent introduction into the system of the mother of a similar substance may explain the convulsions and the symptoms which occur in a certain class of toxemias of pregnancy."

Rosenau and Anderson believed that the placenta must be the source of the toxic material, since typical eclampsia has been observed in patients with hydatidiform mole, in which cases toxic matter of fetal origin could be eliminated as the cause.

These investigators injected fetal blood into non-pregnant and pregnant guinea pigs. After an appropriate interval, a second injection of the same material was given. All of the experiments were negative. The results tended to confirm the clinical observations that the poisons causing toxemia of pregnancy do not come from the fetus.

Rosenau and Anderson next conducted experiments with placental extracts. The placenta, almost at full term, was ground up in a mortar and allowed to "autolyze" about an hour at room temperature. Some of the resulting extract was injected subcutaneously into female guinea pigs. After an interval of twenty-two days, they were again inoculated with a placental extract. This time the placenta was "autolyzed" three hours at 37 C. The second injection of placental extract was followed in all cases by definite symptoms, including convulsions. The authors suggested a possible relationship between toxemias of pregnancy and anaphylaxis.

Murray[40] repeated these experiments, using autolyzed liver, and concluded that his results "seemed to prove that it was the autolysis rather than the pure placental element that caused the anaphylactic symptoms."

Johnstone[41] pointed out that Dreyfuss has shown that the eclamptic placenta undergoes autolysis, due to the excessive activity of its ferments, even during its uterine life. Johnstone performed experiments which "seemed to support the view that there is no evidence of anything in the nature of anapyhlaxis, so far as we at present understand the subject, in the commoner manifestations of the toxemias of pregnancy."

36. Ratner, B.: Allergy, Immunotherapy and Anaphylaxis, Basic Principles and Practice, Baltimore, Williams & Wilkins, 1943.
37. Dale, H. H. and Laidlaw, P. P.: The Physiological Action of B-minazolylethlyamine, J. Physiol. 41:318-344, 1910-11.
38. Dragstedt, C. A.: Anaphylaxis, Physiol. Rev. 21:563-587 (Oct.) 1941.
39. Rosenau, M. J. and Anderson, J. F.: Further Studies on Anaphylaxis, Public Health and Marine Hosp. Serv. of U. S. Hyg. Lab., Bull. No. 43, 1908.
40. Murray, H. L., quoted by Browne, Francis(4).
41. Johnstone, R. W.: An Experimental Study of the Anaphylactic Theory of the Toxaemia of Pregnancy, J. Obst. & Gynaec. Brit. Emp. 19:253-257, 1911.

A review of Johnstone's experiments, however, shows that his conclusions are not entirely justified. In his first experiment he injected the extract of the placenta of eclamptic patients into two female rabbits. According to the known principles of hypersensitivity, any foreign protein, under suitable conditions, is capable of producing anaphylaxis. Thus, no conclusions concerning the role of placenta extracts in toxemia can be drawn from this experiment. Johnstone next injected the tissue fluid of normal human placenta into female rabbits, and obtained slight symptoms. These, too, would be expected from any such introduction of foreign protein. Johnstone next injected pregnant animals with the tissue fluid of healthy placentas obtained from the same species, fresh and unautolyzed. The results were negative. He did not use autolyzed placental fluid. Johnstone considered the possibility that the anaphylactic reactions obtained could be due to the blood serum contained in the preparations. He discounted this possibility, however, on the basis of the small amount of serum injected.

Jegorow[42] stated that there is no toxin, but that the cause of eclampsia is allergy of the pregnant woman, whose organism is gradually sensitized to the normal fetus and placenta. He attached great significance to the allergic condition of the vegetative nervous system.

Erythroblastosis fetalis is known to be an antigen-antibody reaction. Browne[4] felt that, since eclampsia occurs in hydatidiform mole, in which a fetus is absent, and in which there is no fetal blood in the chorionic villi, and since the development of the antibody in the mother depends on the presence of an antigen in the fetal red blood cells, it would be unlikely that there is any association between the Rh factor and pre-eclamptic toxemia. However, the suggestion has been made that the hydatidiform mole may be regarded as an extreme degree of erythroblastosis. The fetus may have been Rh positive and may have caused the development of antibodies in the mother before its death and disappearance.

### *Discussion*

The theory of generalized arteriolar spasm has much clinical and experimental evidence in its support. Most present authorities are strong advocates of it. The only shortcoming of this theory is that it does not explain the cause of the arteriolar spasm. There are no evidences to suggest that any nervous mechanism is involved in the production of this spasm. Evidences have been presented which indicate that the spasm is not due to a toxin. It has been suggested that the toxemias of pregnancy might be due to a sensitization of the mother to some product of conception, possibly the placenta or a product of placental degeneration.

Although argument by analogy is dangerous, a comparison of glomerulonephritis and the toxemias of pregnancy shows numerous resemblances. In both conditions arteriolospasm can very well explain all the clinical symptoms and signs. The pathological changes appear to differ in degree and not in kind. In glomerulonephritis, the sensitizing agent seems to be the streptococcus, or some product of this organism. In toxemia, it has been suggested that some autolytic product of the placenta acts as an antigen to sensitize the maternal organism, and causes an anaphylactic type of reaction. Evidence is presented to show that arteriolar spasm is an essential feature of the anaphylactic reaction. That a physiologically active substance such as histamine is involved in some way in toxemia of pregnancy and also in anaphylactic hypersensitivity is noted.

From the evidence on hand, it appears that the toxemias of late pregnancy are due to an antigen-antibody reaction in the maternal organism. The antigen is thought to be derived from some autolytic product of the placenta, possibly a physiologically active substance such as histamine. Following a certain latent period during which sensitization of the maternal tissue causes the formation of antibody, subsequent contact of the antibody with antigen results in generalized arteriolospasm. The clinical symptoms and signs of toxemia are thus produced.

### *Summary*

1. The toxemia of late pregnancy is defined as that disease dependent on, or peculiar to, pregnancy. Pre-eclampsia and eclampsia are regarded as differing only in the degree of severity of the symptoms and signs.

2. A brief review of the theories of the toxemia of pregnancy is given.

42. Jegorow, B.: (a) *Ist die Eklampsie eine allergische Erkrankung?* Zentralbl. f. Gynaek. 48:2851-4 (Dec. 1) 1934. (b) Die Gesetze der Allergie und Schwangerschaft, Ibid 59:1455-8 (June 22) 1935.

3. The concept of arteriolar spasm as the cause of toxemia is presented. The pathology and pathologic physiology of toxemia are discussed in the light of this concept.

4. The causes of arteriolar spasm are discussed, with emphasis on the roles of pitressin and histamine.

5. Acute glomerulonephritis and toxemia are compared, and the possible role of hypersensitivity in the etiology of acute glomerulonephritis is discussed.

6. The general principles of allergy and particularly of anaphylaxis are given.

7. Hypersensitivity of the anaphylactic type is suggested as playing a role in the pathogenesis of the toxemias of late pregnancy.

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## INCARCERATION OF A MECKEL'S DIVERTICULUM IN A FEMORAL HERNIA

*Report of a Case*

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While the incidence of Meckel's diverticulum is a controversial point, it is known to be a comparatively rare condition. Ladd and Gross[1] state that it is found in 2 to 3 per cent of all individuals examined at autopsy. Strohl and McArthur[2] reviewed necropsy reports by many investigators and found that a Meckel's diverticulum occurred in 1.3 per cent of the cases. Balfour[3] found 15 Meckel's diverticula in 11,107 abdominal operations.

The chief complications of Meckel's diverticulum are: (1) intestinal obstruction, (2) diverticulitis, (3) hemorrhage, (4) intussusception, and (5) incarceration in a hernia. It is with the last complication that this report deals.

Lind[4] credits Lavater with having observed in 1671 the first authentic case of a Meckel's diverticulum contained in a hernial sac. Gray[5] found that up until 1933, 169 such cases had been reported. Of this number, 89 or 52.6 per cent occurred in the inguinal region, 37 or 21.8 per cent in the umbilical region, and 33 or 19.5 per cent in the femoral region. From this report it may be seen that the combination of a femoral hernia and a Meckel's diverticulum is unusual. Even more rare is the incarceration of such a diverticulum in a femoral hernia.

In 1930 Sweet[6] reviewed the literature since 1700 and found only 14 cases reported in which a Meckel's diverticulum was incarcerated in a femoral hernia. He added another case to this group. After a careful review of the literature I found that 6 more cases have been reported since then[7,2], making a total of 21 such cases recorded. The case reported below is the twenty-second case to be recorded in the literature.

*Report of Case*

*History*: I. H., a white female aged 50 years, was admitted to the Abington Memorial Hospital at 11 p.m. on April 4, 1944, with the chief complaint of an irreducible swelling in the right femoral region. She first noticed the swelling about four months previously. At that time it appeared when she coughed, strained or lifted any heavy object, but promptly disappeared when she lay down. The mass gradually increased in size, and twelve hours before admission to the hospital the patient began to have cramp-like pains in her lower abdomen and became aware that she could not reduce the femoral swelling. She became nauseated but did not vomit. A physician was called, and he promptly sent her to the hospital. The past medical history was irrelevant, the patient stating that she had never been in a hospital before, and that her only illnesses had been the usual childhood diseases. The family history was non-contributory.

*Physical examination*: The patient was a middle-aged white female, healthy in appearance and in no evident acute distress. She was somewhat apprehensive. The blood pressure was 130 systolic, 80 diastolic, tem-

1. Ladd, W. E. and Gross, R. E.: *Abdominal Surgery of Infancy and Childhood*, Philadelphia, W. B. Saunders, *1941, pp. 71-82.*
2. Strohl, E. L. and McArthur, S. W.: Incarcerated *Meckel's* Diverticulum in Femoral Hernia, Arch. Surg. 38:783-787 *(April) 1939.*
3. Balfour, D.: Meckel's Diverticulum: A Report of *Fifteen* Cases, J. Minn. M. A. 31:110-112. 1911.
4. *Lind, S. C.: Littre's Hernia*—Meckel's Diverticulum in Hernia Sac, Ohio State M. J. 29:549-551 *(Sept.) 1933.*
5. Gray, H. K.: Meckel's Diverticulum in Hernia, Minnesota Med. *17:68-70 (Feb.) 1934.*
6. Sweet, R. H.: Incarceration of a Meckel's Diverticulum in a Femoral *Hernia; Report of Case with Review* of the Literature, New Eng. J. Med. 202:997-998 (May 22) 1930.
7. (a) Donati, G. S.: Strangulation of Meckel's Diverticulum in Right Crural *Hernia, Policlinico (sez. cher.) 38:* 278-287 (June) 1931.
   (b) Quiri, A.: Meckel's Diverticulum Strangulated in Crural Hernia, Arch. *ital. di chir. 54:16-23, 1938.*
   (c) Ringo, R. E. and Charlton, M. R.: Meckel's Diverti*culum* and Littre's Hernia, Northwest Med. 39:60-61 (Feb.) 1940.
   (d) Marti, T. and Cottet, P.: Incarceration and Perfor*ation of* Meckel's Diverticulum in Left Femoral Hernia, Rev. med. de la Suisse Rom. *62:357-365* (April 25) 1942.

perature 98.8 F., pulse 84, respiratory rate 22. General physical examination was negative except for a swelling in the right femoral region about 1½ inches in diameter. The mass was smooth in contour and moderately tender. The overlying skin was not inflamed. No demonstrable hernia was noted in either inguinal region or in the left femoral region. There was no abdominal tenderness or muscle guarding. The liver and spleen were not palpable. Peristalsis was present and normal. Pelvic and rectal examinations revealed no abnormalities.

*Laboratory studies*: The hemoglobin was 15 Gm. or 97 per cent, and there were 7,600 white blood cells, with 79 per cent polymorphonuclears, 18 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophils. Wassermann and Kahn tests were negative. The blood urea nitrogen was 11 mg. per 100 cc., and the blood sugar was 95 mg. per 100 cc. Urinalysis was negative.

*Operation*: A diagnosis of an incarcerated right femoral hernia was made, and operation was immediately performed under spinal anesthesia. An oblique incision was made directly over the hernia, below Poupart's ligament and parallel to it. The hernial sac was opened and was found to contain 2 ounces of straw-colored fluid. This was removed by suction. In the hernial sac was a diverticulum measuring approximately 4.8 cm. in length and 1.8 cm. in diameter. It was moderately injected throughout, and the tip was brownish-black in appearance. The femoral ring was so narrow that the diverticulum was constricted by it. The ileum was delivered and was found to be normal in appearance. The diverticulum was located approximately 18 inches proximal to the ileocecal area. A narrow mesentery attached to the diverticulum was clamped, cut, and ligated at the base of the diverticulum. The diverticulum was then removed with the cautery, and the stump was covered by the Parker-Kerr aseptic technique. Chromic catgut was used throughout. The small intestine was replaced in the peritoneal cavity. The hernial sac was ligated at its base and the redundant portion removed. Gimbernat's ligament was repaired with interrupted wire sutures, and the femoral ring was then closed with similar wire sutures. Michel clips were used to close the skin.

*Postoperative course*: The postoperative course was smooth and uneventful. At no time did the patient become nauseated or suffer abdominal pain. She had a slight elevation of temperature for twenty-four hours, but following this the temperature returned to normal and remained thus. The incision healed perfectly, and the skin clips were removed on the fifth postoperative day. On the sixth postoperative day the patient was placed on house diet. She was allowed out of bed twelve days following operation, and was discharged on the fourteenth postoperative day. When she was examined two months and six months after discharge from the hospital, her condition was satisfactory.

*Pathologic report*: The surface of the diverticulum was smooth and glistening and blue-grey to tan in color. The tip was brownish-black in appearance. On section the mucosa was found to be covered by a small amount of tan, mucus-like material. The mucosa of the distal half of the specimen was decidedly reddened. On microscopic examination, the section was that of small intestine showing extensive hemorrhages into the mucosa and submucosa, with marked round cell and plasma cell infiltration. At least 90 per cent of the glandular epithelium was absent. The diagnosis was acute catarrhal inflammation of Meckel's diverticulum.

### *Comment*

The choice of surgical procedure in this type of case is based entirely on the circumstances present. If the base of the diverticulum is small, the best procedure is probably ligation and inversion of the stump as in an appendectomy. If the base is wide, removal of the diverticulum with transverse closure should be done. Gray[5] advocated entero-anastomosis if there is any doubt as to the patency of the lumen of the intestine.

### *Summary*

A case of incarceration of Meckel's diverticulum in a femoral hernia with recovery is reported. A review of the literature disclosed only 21 such cases previously reported.

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**The Privacy of Family Problems.** The wise physician will not write down a woman's secret story of sexual unhappiness or perhaps family tragedy as she tells it. When I start trying to draw out this part of the story, or when I sense that the patient wants to talk to me about secret things, I put away the history sheet and say, "This is off the record." We physicians would hate to have any such secrets of ours put down and left lying around, especially in a large institution where desk girls, nurses, interns, and others can pick up the record and read it.—Alvarez, Walter C.: Nervousness, Indigestion, and Pain, New York, Paul B. Hoeber, 1943, p. 64.

# THE CARDIAC GLYCOSIDES

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*and*
EDWARD S. ORGAIN, M.D.

It is generally agreed that the ideal digitalis preparation for clinical use would be a pure chemical compound of known composition, reliable potency and low cost, which would be readily and uniformly absorbed from the gastrointestinal tract and which could be measured gravimetrically rather than standardized biologically. Toward the attainment of this ideal drug much chemical, pharmacologic, and clinical investigation has been devoted in recent years to the potent active principles of digitalis, primarily the purified glycosides of the drug. While no single glycoside satisfies all the criteria for the perfect preparation, the glycosides as a whole have a small yet important position in the therapy of heart disease. Because of their great usefulness in certain disturbances of cardiac physiology, it is incumbent upon the physician to become familiar with their structure, the indications for their use, and the methods of administration. To present these facts briefly and practically is the purpose of this paper.

## *Structure and Derivation*

The therapeutic effect of standard digitalis leaf preparations depends on certain organic chemical compounds, most of which have been isolated in the pure state. These compounds are known as the *cardiac glycosides**, and their therapeutic and toxic effects are those of digitalis. The essential constituents of a cardiac glycoside (fig. 1) are: (1) a *sterol nucleus*, (2) an *unsaturated butyrolactone ring*, and (3) a *desoxy sugar*. The unsaturated butyrolactone ring on C-17 is essential to the cardiac action of the glycoside[2]. When the desoxy sugar is removed, the resulting compound is known as a *genin (aglycone)*. It is cardio-active, but less so than when combined with a *desoxy sugar*[2] such as digitoxose.

BASIC STRUCTURE OF A CARDIAC GLYCOSIDE

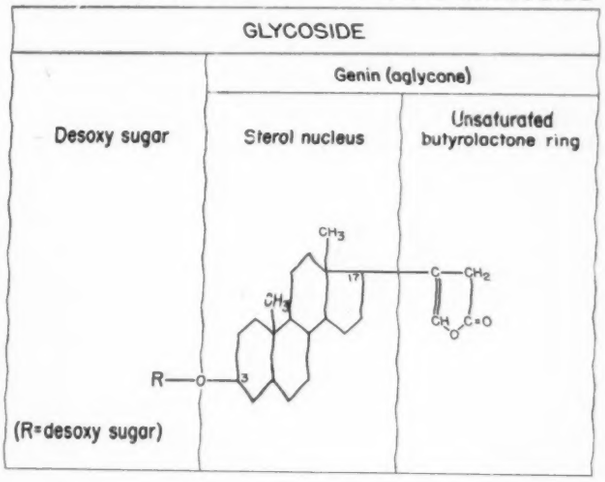


Fig. 1. Basic structure of a cardiac glycoside.

Many of the glycosides contain, in addition to the three essential constituents, a molecule of *glucose*, which does not enhance potency and in most cases decreases it[2]. The glycosides of Digitalis lanata contain also an *acetyl radical*, not present in those of Digitalis purpurea.

The two foxglove plants from which therapeutic digitalis preparations are made are Digitalis purpurea and Digitalis lanata. Most of the whole-leaf preparations are derived from Digitalis purpurea, while Digitalis lanata is the principal source of the crystalline glycosides, both because of its greater yield and because it contains an important glycoside, *lanatoside C*, not present in Digitalis purpurea. Pure glycosides also are obtained from Strophanthus gratus (ouabain), Strophanthus kombe, and squill. It is seen from table I that the glycosides *digitoxin* and *gitoxin* are common to both foxglove plants, while *gitalin* occurs only in Digitalis purpurea, and *digoxin* occurs only in Digitalis lanata. Reference to table I will serve to clarify the breakdown of Digitalis purpurea and Digitalis lanata into their respective pure principles[3].

## *Comparison with Digitalis*

Digitalis leaf contains a variable mixture of glycosides, each with a different rate and degree of intestinal absorption. In general, only about one-fifth of the active material

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* The combination of a sugar with an organic compound of another chemical class is called a *glycoside*. The term *glucoside* should be reserved for those substances yielding the specific sugar, glucose(1a).

1. (a) De Graff, A. C. and Batterman, R. C.: Recent Advances in Digitalis Therapy, with Particular Attention to the Use of Pure Glycosides, M. Clin. North America 26:929-942 (May) 1942.
(b) Freedberg, A. S. and Blumgart, H. L.: Digitalis, Edema, and Diuretics, New England J. Med. 227:874-880 (Dec. 3) 1942.
2. De Graff, A. C., Paff, G. H., and Lehman, R. A.: The Quantitative Effect of Fifteen Chemically Related Glycosides and Genins on the Embryonic Chick Heart, J. Pharmacol. and Exper. Therap. 72:211-225 (June) 1941.
3. Stoll, A.: The Cardiac Glycosides, London, The Pharmaceutical Press, 1937.

THE BREAKDOWN OF DIGITALIS LANATA AND DIGITALIS PURPUREA.
(MODIFIED FROM STOLL---THE CARDIAC GLYCOSIDES---LONDON, 1937)

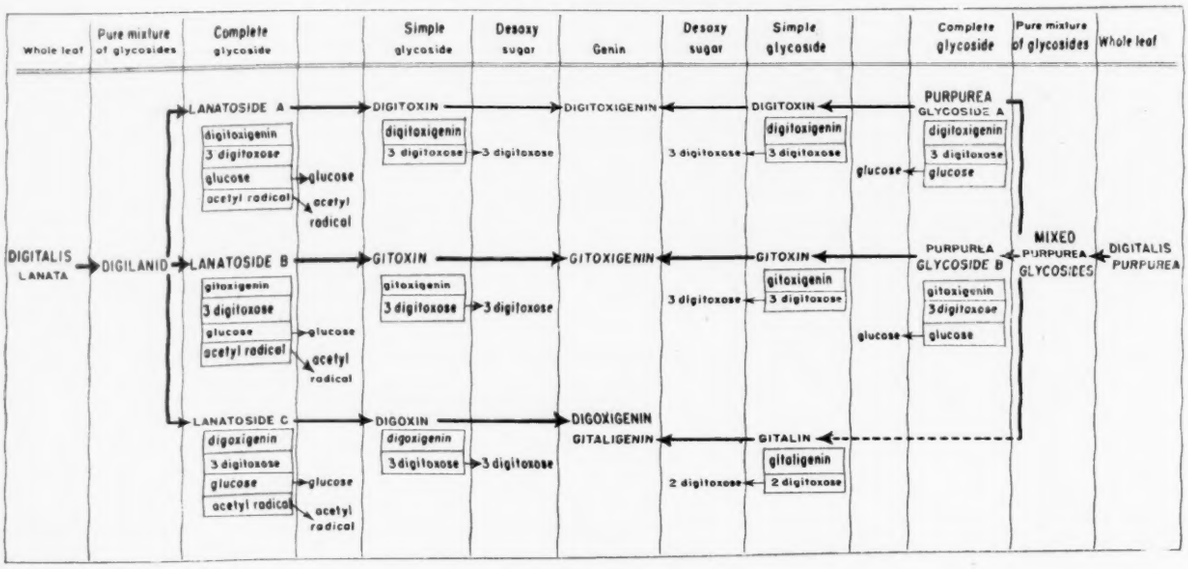


Table 1

present in whole-leaf preparations of digitalis plays a part in producing the final therapeutic effect of oral doses. This fact has been shown repeatedly by comparisons of the effects of oral and intravenous doses[4]. Since the glycosides are pure chemicals, they may be measured simply by weight; for, once their potency is determined, biologic assay is no longer necessary[1].

It is important to point out that *"cat unit" potency of pure glycosides is not comparable to "cat unit" potency of digitalis leaf.* For example, 3 "cat units" of digitoxin have the clinical potency of 20 "cat units" of digitalis. While 20 "cat units" of digitalis leaf represent a full therapeutic dose, the administration of 20 "cat units" of digitoxin to a patient would prove highly toxic and probably fatal. The "cat unit" is not recognized by the U. S. Pharmacopeia, and the continued use of the term serves no useful clinical purpose. The glycosides are measured gravimetrically and are prescribed safely in terms of the weight of the drug.

The rate and degree of absorption from the intestinal tract are different for each glycoside. When the glycosides are given intravenously the time required for the onset of their action is practically the same for each one, and is approximately five to twenty minutes. The rate of elimination varies with the individual substances. When they are injected intravenously, cardiac glycosides should be administered slowly over a period of several minutes, in order that a maximum proportion of the active substance may be fixed in the myocardium.

The chief advantages of the pure cardiac glycosides over the ordinary digitalis leaf may be listed as follows:

1. Pure crystalline preparations, their potency once established, may be measured by weight; they need not be assayed biologically, and do not deteriorate.

2. Intestinal absorption is uniform for each individual glycoside, while digitalis leaf contains a variable number of glycosides with different degrees and rates of absorption.

3. Oral digitalization may be accomplished more rapidly with pure glycosides[5a] than with whole-leaf preparations (see digitoxin, below).

4. The pure principles may be given intravenously to meet the need for immediate action in certain cases.

### *Intravenous Use of Glycosides*

The pure digitalis principles should be administered intravenously only when this route is definitely indicated and when one

4. Gold, H.: Digitalis and Some of Its Derivatives, II. Science 97:150 (Feb. 12) 1943.

5. (a) Gold, H., Kwit, N. T., Cattell, M., and Travell, J.: Studies on Purified Digitalis Glycosides: IV. The Single Dose Method of Digitalization, J.A.M.A. 119: 928-932 (July 18) 1942.
(b) Gold, H., and others: Clinical Studies on Digitoxin (Digitaline Nativelle), with Further Observations on Its Use in the Single Average Full Dose Method of Digitalization, J. Pharmacol. and Exper. Therap. 82: 187-195 (Oct.) 1944.

can be certain that the patient has not received digitalis within the past two weeks. In properly selected cases, however, intravenous administration of a cardiac glycoside may be life-saving. Intravenous administration is indicated whenever rapid digitalis action is desirable or imperative. Several examples are listed below:

1. Acute left ventricular failure with acute pulmonary edema.

2. Certain cardiac arrhythmias, including auricular fibrillation or auricular flutter, with or without acute congestive heart failure, when immediate slowing of the ventricular rate becomes necessary; auricular tachycardia which may be aborted by accelerated digitalization.

3. The presence of complicating conditions which render it impossible or impractical to give digitalis by mouth; here the intramuscular route* also may be used.

4. The necessity for emergency surgical procedures in patients with severe heart strain, decompensation, or auricular fibrillation.

### *Preparations of Glycosides*

For obvious reasons separate discussion of each of the glycosides is impractical and unnecessary. Several individual preparations of the cardiac glycosides have been chosen for presentation because they have special virtues and have proved to be of clinical value. It is recommended that each physician select one of these preparations for exclusive use until he has attained comfortable familiarity with the drug.

#### *Digitoxin*

Digitoxin is a pure crystalline glycoside obtained commercially from Digitalis purpurea. It is marketed as *Digitaline Nativelle* (Fougera) and as *Purodigin* (Wyeth). By weight, digitoxin has a potency about one thousand times as great as crude digitalis leaf—that is, 0.1 mg. of digitoxin is equivalent to about 0.1 Gm. of digitalis U.S.P. XII. It is unique among the glycosides in that it is rapidly and completely absorbed from the intestinal tract[5a], and a given amount is therefore equally effective whether administered orally or intravenously. Furthermore, the entire digitalizing dose may be given orally at one time, full effects being obtained within six hours[5]. Whole leaf digitalis cannot be used in this manner because such a large single dose produces nausea and vomiting by local gastric irritation[5a].* Digitoxin, therefore, is ideal for rapid oral digitalization. It is eliminated slowly, and is probably the principle responsible for the slow excretion of crude digitalis.

The usual digitalizing dose is approximately 1.2 mg.[7] This may be given *orally* as a single dose[5a] or in divided doses, or it may be administered *intravenously* by injecting one-half (0.6 mg.) initially, and the remaining 0.6 mg. after four to six hours. The maintenance dose is about 0.2 mg. daily, but more may be required by certain patients.

#### *Digilanid*

Digilanid (Sandoz) is a mixture of the pure crystalline lanatosides (A, B, and C) obtained from Digitalis lanata. These are present in digilanid in the constant ratio of 47:17:36. The potency of digilanid is such that 0.2 mg. is equivalent to 0.065 Gm. digitalis U.S.P. XI[8]. Digilanid has no known advantages over the single crystalline glycosides.

The total *oral* digitalizing dose ranges from 4.95 to 6.6 mg. given over a period of approximately three days. The maintenance dose is about 0.33 mg. daily[9]. For *intravenous* use, the manufacturer recommends the slow administration of 0.8 mg. of the drug.

#### *Lanatoside C*

This is a pure crystalline complete glycoside obtained from Digitalis lanata and is the precursor of the simple glycoside, digoxin. It is marketed as *Cedilanid* (Sandoz). Lanatoside C is slowly and imperfectly ab-

* The cardiac glycosides are irritant and too painful for subcutaneous injection; while the intramuscular route may be used, pain and tenderness often result.

* The nausea and vomiting produced by overdigitalization with repeated small doses, on the other hand, arises from afferent impulses from the heart(6).

6. (a) Hatcher, R. A., and Eggleston, C.: The Emetic Action of the Digitalis Bodies, J. Pharmacol. and Exper. Therap. 4:113-134, 1912.
(b) Hatcher, R. A., and Weiss, S.: The Seat of the Emetic Action of the Digitalis Bodies, Arch. Int. Med. 29: 690-704 (May) 1922.
7. Gold, H., Kwit, N. T., and Cattell, M.: Studies on Purified Digitalis Glucosides: I. Potency and Dosage of "Digitaline Nativelle" by Oral Administration in Man, J. Pharmacol. and Exper. Therap. 69:177-197 (July) 1940.
8. (a) Batterman, R. C., Holman, D. V., and De Graff, A. C.: The Therapeutic Effectiveness and Potency of Digilanid in the Treatment of Congestive Heart Failure, Ann. Int. Med. 14:2058-2072 (May) 1941.
(b) Adams, W., and Gregg, L. A.: Clinical Comparison of the Crystalline Glucosides of Digitalis Lanata (Digilanid) and the Powdered Leaf of Digitalis, Am. Heart J. 19:576-586 (May) 1940.
9. La Place, L. B.: The Relative Clinical Potency of Digitalis U.S.P. X, Digitalis U.S.P. XI, and Digilanid, Am. Heart J. 26:536-541 (Oct.) 1943.

sorbed from the intestinal tract[10], and the oral and intravenous doses are therefore different. In contrast to digitoxin, this glycoside is eliminated rapidly[10], so that toxic effects from overdosage with lanatoside C disappear within a matter of hours.

The conclusion[11] that lanatoside C has a greater margin of safety than other cardiac glycosides was not confirmed by the studies of Gold and Cattell[12]. These investigators found the same degree of toxicity for each of the preparations studied.

The following scheme is recommended for *oral* digitalization: First day, 3.75 mg.; second day, 2.5 mg.; third day, 1.0 mg., followed by approximately 1 to 1.25 mg. per day[13a] as a maintenance dose. The *intravenous* digitalizing dose is about 1.6 mg.[13]; this may be given at one time, or divided into two equal doses and given at four to twelve hour intervals. The parenteral maintenance dose is about 0.1 to 0.2 mg. daily.

*Digoxin*

*Digoxin* (Burroughs-Wellcome) is a pure crystalline glycoside obtained from Digitalis lanata, and is a breakdown product of the complex glycoside, lanatoside C. Digoxin is excreted rapidly, as might be expected from its relation to lanatoside C. For *oral* digitalization the following method[14] is suggested: an initial dose of 1.5 mg., followed by 0.75 mg. at six-hour intervals until the desired therapeutic effect has been produced. A daily maintenance dose of 0.5 to 0.75 mg. then may be given. Schwab[15] notes that the rapid excretion of this glycoside may make maintenance difficult, and states that 1 mg. or more may be required each day. For *intravenous* use, 1.5 mg., followed in six hours by an additional 0.5 mg., produces rapid digitalization[15].

*G-Strophanthin*

This is a pure crystalline glycoside obtained from Strophanthus gratus and marketed as *Ouabaine* (Fougera). For many years ouabain was used as the reference standard in the biologic assay of digitalis. It is very poorly absorbed from the intestinal tract and therefore should not be given orally. There is no convincing evidence that preparations of strophanthin are superior to those of digitalis.

Ouabain may be given *intravenously* in a dose of 0.5 mg., followed by 0.1 mg. every thirty minutes until the full effect is obtained[16]. The average ouabainizing dose lies in the vicinity of 1 mg. We have not been able to find a satisfactory maintenance dose recorded, but ordinary digitalis should be adequate. Ouabain is eliminated rapidly[16], and is practically all excreted by the fifth day after injection. Because of this rapid elimination and the fact that orally administered digitalis does not take effect for two to five hours[17], a method has been devised for combining ouabain with digitalis[18]. Five-tenths milligram of ouabain is administered *intravenously* at the same time that 0.4 to 0.8 Gm. of digitalis is given *orally*. After twenty-four hours, the daily maintenance dose of digitalis is started. The maximal effect of the digitalis is thus obtained as the effect of the ouabain decreases, and a smoothly progressing glycoside saturation results.

*K-Strophanthin*

This is a mixture of the purified amorphous glycosides of Strophanthus kombe. K-strophanthin is marketed as *Strophanthin-K* (Abbott, Burroughs-Wellcome). Strophanthin often causes a marked increase in sweating[19], and weight loss due to extrarenal water excretion may be considerable. Three-tenths milligram of strophanthin-K is equivalent to 0.17 mg. of ouabain.

The drug may be given by slow *intravenous* injection (never orally) in a dose of 0.26 to 0.65 mg. No more than 0.65 mg. should be administered in a twenty-four hour period. A suggested dosage[19] is 0.3 mg. once in twenty-four hours, or 0.5 mg. if fail-

10. Kwit, N. T., Gold, H., and Cattell, M.: Studies on Purified Digitalis Glucosides: II. Potency and Dosage of Lanatoside C in Man, *J. Pharmacol. and Exper. Therap.* 70:254-269 (Nov.) 1940.
11. Moe, G. K. and Visscher, M. B.: Studies on the Native Glucosides of *Digitalis Lanata* with Particular Reference to Their Effects upon Cardiac Efficiency and Their Toxicity, *J. Pharmacol. and Exper. Therap.* 64:65-85 (Sept.) 1938.
12. Gold, H. and Cattell, M.: Status of Bioassay of the Digitalis Group, *Science* 93:197-201 (Feb. 28) 1941.
13. (a) Fahr, G. and LaDue, J.: A Preliminary Investigation of the Therapeutic Value of Lanatoside C, Am. Heart *J. 21:133-150 (Feb.) 1941.*
(b) La Due, J. S.: Intravenous Use of Digitalis Glycosides, South. M. J. 36:124-133 (Feb.) 1943.
14. Rose, O. A., Batterman, R. C., and De Graff, A. C.: Clinical Studies on Digoxin, a Purified Digitalis Glycoside, Am. Heart J. 24:435-457 (Oct.) 1942.
15. Schwab, E. H.: Clinical Observations on Pure Glucoside of Digitalis Lanata, Digoxin, Texas State J. Med. 35:619-622 *(Jan.) 1940.*
16. Wyckoff, J. and Goldring, W.: Intravenous Injection of Ouabain in Man, Arch. Int. *Med. 39:488-497 (April) 1927.*
17. (a) Pardee, H. E. B.: Rate of Absorption of Digitalis *from Gastro-Intestinal* Tract, J.A.M.A. 75:1258 (Nov. 6) 1920.
(b) Eggleston, C. and Wyckoff, J.: The Absorption of *Digitalis, Arch. Int. Med. 30:133-157* (Aug.) 1922.
18. Batterman, R. C., Rose, O. A., and De Graff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, Am. Heart J. 20:443-453 (Oct.) 1940.
19. Brams, W. A., Golden, J. S., Sanders, A., and Kaplan, L. G.: Observations on Toxicity and Clinical Value of Strophanthin, Ann. Int. Med. 13:618-628 (Oct.) 1939.

ure is severe. Subsequent daily injections of 0.3 mg. are usually enough for maintenance. Strophanthin-K is said to be almost wholly excreted within twenty-four hours, and a method for combining its use with that of digitalis has been described[20]. A 0.25 mg. dose of strophanthin-K in 10 cc. of normal saline is *injected slowly* (over a 3-minute period) *into the vein.* Immediately following this injection 0.4 to 0.5 Gm. of digitalis is given *orally.* Subsequently 0.2 Gm. of digitalis is given three times daily until full effect is manifest, and then a daily maintenance dose (0.1 Gm.) of digitalis is begun.

*Summary*

The purified cardiac glycosides, which represent the potent, active constituents of digitalis leaf, have already assumed an important and useful position in the therapy of heart disease. The structure, derivation, individual characteristics, indications for use, and methods of administration of a few of the more important glycosides have been discussed, in the hope that the correlation of this information will prove of practical value to the general physician.

20. Garcia, J. E. and Goldman, B. A.: The Combined Use of Strophanthin-K and Digitalis in the Treatment of Congestive Heart Failure, Am. Heart J. 26:20-23 (July) 1943.

## AN ANALYSIS OF THREE THOUSAND SEVEN-HUNDRED-ONE ADMISSIONS TO THE UNITED STATES PUBLIC HEALTH SERVICE MEDICAL CENTER IN DURHAM NORTH CAROLINA*

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*and*
GEORGE FEIN, M.D.**
DURHAM

*We believe that the medical profession of* North Carolina will be interested in the activities of the U. S. Public Health Service Medical (Rapid Treatment) Center in Durham, North Carolina, for the first seventeen months of its operation—*the period from* November 1, 1943, to March, 1945. The majority of the 3,701 patients admitted to the institution during this period were referred from health departments of the cities and counties in the eastern part of the state. The primary purpose of this report is to analyze the occurrence of the various diseases in these patients, to correlate their age, race, and sex, and to discuss the methods by which the diagnoses were made.

Through the excellent cooperation of the state and local health departments there has been a gradual increase in the number of admissions to the rapid treatment center, so that the rate now exceeds 350 patients a month. The admissions for syphilis have far exceeded those for gonorrhea, although many patients referred for syphilis were also found to have gonorrhea. No venereal disease could be found in 158 patients (4.3 per cent). Over two thirds of these were babies or small children accompanying their mothers, and were not referred for examination. The remainder were patients who had previously received adequate treatment for syphilis, and patients with a variety of dermatological problems who were referred to us for diagnosis.

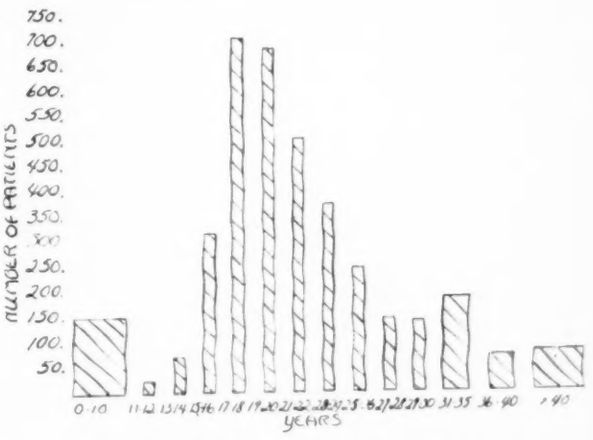



**Fig. 1. Admissions according to age.**

The ages of the patients varied from 1 week to 75 years (fig. 1). Of the 151 children admitted below the age of 10, the greater number had no venereal disease; the majority of those infected had congenital syphilis, while 6 had acquired the disease. Forty and two tenths per cent of the total admissions were patients between the ages of 17 and 20 years, inclusive; 70 per cent were between 15 and 24 years, inclusive; 26.4 per cent were 25 years or over.

As table 1 shows, the colored admissions outnumbered the white by more than three to one, while the ratio between the colored and white females admitted was four to one.

* Acknowledgment for the use of this material is given Passed Assistant Surgeon Evert A. Swensson and Surgeon (R) Samuel Fisher, Medical Officers in Charge during this period.

**Passed Assistant Surgeon (R), U. S. Public Health Service.

There were about two female patients to every male admitted, and approximately half of the patients were colored females. White males made up the smallest number.

**Table 1. Admissions According to Race and Sex**

| | *Colored* | | *White* | | *Total* | |
|---|---|---|---|---|---|---|
| | *Number* | *Per cent* | *Number* | *Per cent* | *Number* | *Per cent* |
| Males | 1067 | 28.8 | 353 | 9.5 | 1420 | 38.3 |
| Females | 1809 | 48.9 | 472 | 12.8 | 2281 | 61.7 |
| TOTAL | 2876 | 77.7 | 825 | 22.3 | 3701 | 100. |

### *Syphilis*

Of the 3,701 patients referred to the Center, 2,665, or 72 per cent, were found to have syphilis. Twenty-eight and one-half per cent of these were found also to be infected with gonorrhea, and 3.6 per cent had coexistent lymphogranuloma venereum, chancroid, granuloma inguinale, or a combination of these diseases.

*Methods of diagnosis*

(1) *Darkfield examination*

The darkfield examination was extensively used as an aid in the diagnosis of primary and secondary syphilis. All examinations were performed by a competent physician. If Treponema pallidum could not be demonstrated in the lesions, lymph node punctures were done when feasible[1]. When the darkfield examination was positive the diagnosis of syphilis could be made without waiting for the report of the serologic test, and the presence of a negative serologic reaction, as in sero-negative primary syphilis, did not delay the diagnosis and the institution of treatment.

**Table 2. Results of Darkfield Examinations**

| *Stage* | *No. Admitted with No Previous Treat.* | *Darkfield Exam. Pos.* | *Neg.* | *Not Done* |
|---|---|---|---|---|
| Sero-neg. primary | 31 | 31 | 0 | 0 |
| Sero-pos. primary | 101 | 55 | 41 | 5 |
| Secondary | 504 | 434 | 53 | 17 |

Table 2 shows the results of the darkfield examinations performed on the patients with primary and secondary syphilis who had not been previously treated. Nineteen and one-half per cent of the total number of patients with syphilis had darkfield positive lesions. More than 77 per cent of the patients with primary syphilis had a positive darkfield examination.

1. (a) Agee, O. F.: Dark-Field Examination of Material from Lymph Node Puncture, Am. J. Syph., Gonor. & Ven. Dis. 28:37-58 (Jan.) 1944.
   (b) Loveman, A. B., and Morrow, R. P., Jr.: The Value of Dark-Field Examination of Lymph Nodes in the Diagnosis of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. 28:44-56 (Jan.) 1944.

(2) *Serologic tests*

The most important and most widely used laboratory examination for syphilis is the serologic test. The serologic reaction depends on an antibody-like substance elaborated within the tissues of the host in response to the infectious agent. The substance formed in response to T. pallidum is known as reagin. A positive reaction can generally be accepted as evidence of spirochetal invasion, though other diseases may produce a reagin which gives a positive serologic reaction.

Qualitative tests are the most generally used, but they give no information as to the amount of the reagin present. Quantitative tests, performed on serial dilutions of serum, indicate the amount of reagin present. The trend of the titer is essential in the early diagnosis of darkfield-negative primary and congenital syphilis, and in the study of patients who have had rapid treatment for syphilis, to determine whether a cure or a relapse can be anticipated. This test is perhaps the most important procedure available in distinguishing between true positive and biologic false positive serologic reactions.

Fifty-one patients, or 1.8 per cent of those admitted for treatment of syphilis, were found to have biologic false positive serologic reactions. After extensive study these patients were returned to the local health departments for three months' observation and serologic testing. A recent review shows that only one of these patients was subsequently treated for syphilis.

(3) *Clinical history and examination*

Patients with a reliable history of inadequate treatment were presumed to have syphilis. Fifty-six and six tenths per cent of the patients had received treatment before entry. The majority had had less than twenty injections of an arsenical and twenty injections of bismuth.

A lumbar puncture was performed on all patients to eliminate the possibility of neurosyphilis. If a careful examination, with particular emphasis on the cardiovascular and central nervous systems, disclosed no abnormalities attributable to syphilis, the disease was considered to be latent. Cases of latent syphilis were classified as early or late, depending on the patient's age or the duration of the disease. Cases of more than four years' duration were denominated as late latent syphilis. When the date of onset of the

infection could not be satisfactorily established, the age of 25 in Negroes and 30 in white patients was arbitrarily used to separate early and late latency. In patients with congenital syphilis, 2 years was the age used for dividing early and late latency.

### Stages of syphilis

**Table 3. The Occurrence of Stages of Syphilis**

| Stage of Syphilis | No. Cases | Percent of Total Admissions |
|---|---|---|
| Primary, sero-neg. | 42 | 1.6 |
| Primary, sero-pos. | 137 | 5.1 |
| Secondary | 665 | 25.1 |
| Relapse—clinical | 89 | 3.3 |
| Relapse—serological | 8 | 0.3 |
| Reinfections | 3 | 0.1 |
| Early latent | 1411 | 53.1 |
| Congenital—early latent | 38 | 1.4 |
| Late latent | 114 | 4.2 |
| Congenital—late latent | 54 | 2.0 |
| Cardiovascular | 4 | 0.1 |
| Central nervous system | 97 | 3.6 |
| Other late | 3 | 0.1 |
| TOTAL | 2665 | 100. |

Table 3 illustrates the occurrence of the various stages of syphilis. Ninety per cent of the patients admitted had early syphilis. In this group 6.7 per cent were cases of primary syphilis, of which approximately a fourth were sero-negative; 28.7 per cent were cases of secondary syphilis, of which 12 per cent were recurrent; 60.7 per cent were cases of latent syphilis, of which 90 per cent were early latent.

Patients with late syphilis made up a little more than 3 per cent of the total admissions. Neurosyphilis was the most frequent manifestation of late syphilis, and only 10 per cent of the 97 cases of central nervous system involvement had been recognized before admission. The vast majority were asymptomatic.

### Relapse and reinfection

As is shown in table 3, 3.3 per cent of the admissions were for clinically relapsing syphilis. Many were patients who had previously received intensive treatment in our institution. It is the consensus that a greater number of reinfections will occur following intensive therapy than after standard treatment schedules, since the protective factor of prolonged treatment is lost. Patients treated by us are requested to have monthly quantitative serologic tests. A rapid rise in titer, especially after a previous negative reaction, is an indication for reexamining the patient. In 90 per cent of such cases darkfield positive lesions were found.

In patients returning with new infectious lesions the question arises whether reinfection or relapse has occurred. Some of the so-called relapses are undoubtedly reinfections. Only 3 of our patients fulfilled the following rigid criteria for the diagnosis of reinfection[2]:

(1) An original infection, with a darkfield positive lesion.
(2) Adequate treatment for the original infection.
(3) Negative spinal fluid and achievement of sero-negativity which was maintained for six months.
(4) A new darkfield positive sero-negative chancre in a site different from the original one and accompanied by a bubo.
(5) A definite history of exposure for the second infection.

### Gonorrhea

A total of 1,457 patients were admitted during this period with a diagnosis of gonorrhea — 39.4 per cent of all admissions. Seven-hundred and sixty-one, or 52.2 per cent of these, had coexistent syphilis[3], lymphogranuloma venereum, chancroid, granuloma inguinale, or various combinations of these diseases. Over half of the patients with gonorrhea had been previously treated with sulfonamides. Complications occurred in 7.2 per cent of our cases. The most frequent were pelvic inflammatory disease in the female and prostatitis and epididymitis in the male.

Epidemiologic, clinical and bacteriologic evidences were considered in making the diagnosis of gonorrhea. It is admitted that epidemiologic evidence is not always trustworthy and that clinical evidence is only presumptive, but in view of the public health problem which these patients present, they were treated with penicillin on the least suspicion. The use of the drug is simple and involves little risk. However, in 1,027 cases, or 70.5 per cent of all the admissions for gonorrhea, the gonococcus was recovered by cultural methods. The cultures were made from material obtained from the urethra and cervix in the female and from the urethra, prostatic fluid, and urine sediment in the male. The material was streaked directly on chocolate agar media (Difco), to

2. (a) Wile, U. J.: Personal communication.
(b) Neilson, A. W., Blaney, L. F., Stephens, L. J., and Maxwell, R. W.: Intensive Chemotherapy of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. 28:553-570 (Sept.) 1944.

3. Guthrie, N. W.: Syphilis in Gonorrhea Patients and Contacts, Am. J. Syph., Gonor. & Ven. Dis. 28:583-587 (Sept.) 1944.

which Difco supplement A had been added. The plates were incubated for forty-eight hours at 35 C. in an atmosphere containing approximately 10 per cent carbon dioxide. They were then inspected and sprayed with 1 per cent para-aminodimethylaniline monohydrochloride for the oxidase reaction. The oxidase-positive colonies were picked, spread, and stained by Hucker's modification of Gram's stain. The diagnosis of gonorrhea was made when gram-negative diplococci, morphologically resembling gonococci, were obtained from the oxidase-positive colonies.

### *Granuloma Inguinale*

The diagnosis of granuloma inguinale was based on the demonstration of Donovan bodies in spreads made from a minute piece of granulation tissue obtained from the border of the lesion. The site was first cleansed of exudate; a tiny piece of granulation tissue was removed with a small bone curette and was then macerated between two slides, dried, and prepared with Wright's stain. Mature intracellular Donovan bodies should be found before a positive diagnosis is made, even though long searches are frequently necessary to demonstrate them. The Donovan bodies can also be demonstrated by the special staining of microscopic sections.

There were 42 cases of this disease (1.1 per cent of the total), only 13 of which were a single disease entity. It occurred only in the Negro and twice as frequently in the female as in the male. In general, the patients were older than those seen with other venereal diseases. The ulcerative, exuberant, and cicatricial clinical types[4] were observed, in this order of frequency.

Several cases were seen which are of epidemiologic interest. A, a colored male, and his consort, B, were both found to have granuloma inguinale. We subsequently discovered another colored girl, C, who had occupied a hotel room adjoining that of B, to be infected with the same disease. Sex contact with A was denied by C, but this denial was open to question, since the three were good friends. Donovan bodies were demonstrated in spreads of the granulation tissue in the three patients. Another case was that of a brother and sister who had far advanced granuloma inguinale. They denied sexual contact with each other, but the woman said that she frequently wore her brother's pants. Another patient with extensive granulomatous lesions around the external genitalia and extending into the vagina was pregnant, and eventually gave birth to a normal healthy child. To date the infant shows no evidence of having acquired or inherited the disease.

No biologic false positive reactions were encountered in patients with granuloma inguinale. Syphilis was the most frequent coexistent disease. Superimposed malignancy was not noted in any of our cases. Many were complicated with fusospirochetosis.

### *Lymphogranuloma Venereum*

The diagnosis of lymphogranuloma venereum was based mainly on a positive Frei skin test in the presence of typical clinical findings. Lygranum[5] was used as the antigen.

The technique of the lygranum skin test consisted of injecting intradermally, at separate sites on the forearm, 0.1 cc. of the killed virus antigen and an equal amount of normal chick embryo yolk for control. Readings were made in forty-eight hours and, if the test was doubtful at the end of this period, again in seventy-two hours. Five millimeters of induration was considered a positive reaction. When a negative skin reaction occurred in the presence of suspicious lesions, the test was repeated in a week. Ten to fifteen days is the approximate time required for the test to become positive after the infection is acquired[4]. It is believed that skin sensitization for the antigen is permanent following an attack of the disease.

The Frei test was positive in 103 patients showing lesions—2.8 per cent of the total admissions. In only 9 cases—approximately 10 per cent—did lymphogranuloma venereum occur as a single disease entity. Biologic false positive serologic reactions were occasionally encountered in these cases. The remaining patients with positive Frei tests had coexistent venereal diseases, and the significance of the skin reaction in this group is limited. The lesions in such cases might be due to the coexistent venereal disease, and the positive skin reaction to the patient's having had lymphogranuloma venereum at another time in his life.

The various clinical types of lymphogranuloma venereum were observed. The pri-

4. Greenblatt, Robert B.: Management of Chancroid; Granuloma Inguinale and Lymphogranuloma Venereum in General Practice. Ven. Dis. Inform. (Supp. 19) pp. 1-43, 1943.

5. Rake, G., McKee, C. M., and Shaffer, M. F.: Agent of Lymphogranuloma Venereum in Yolk-Sac of Developing Chick Embryo, Proc. Soc. Exper. Biol. & Med. 43:332-334 (Feb.) 1940.

mary lesion, which is a small, superficial, evanescent one, was seen in only a few instances. It was identified only after the patient had developed the large, firm inguinal buboes of the more common inguinal type of lymphogranuloma venereum. These buboes tend to suppurate, break down, and drain through the skin for protracted periods. Various ulcerative forms of the genital type were also seen. In 2 males we observed the bubonulus type—multiple small abscesses, with draining sinuses, occurring along the course of the lymphatics of the penis. In one case extension to the abdominal wall and the lateral aspect of one thigh ensued. No rectal strictures were encountered, but we did see many patients with nontender, polypoid, rubbery tabs about the anal orifice which were believed to be the residuum of the healed anal type.

*Chancroid*

The diagnosis of chancroid was made either by demonstrating Hemophilus ducreyi in smears from the lesions or by the skin test with an antigen made of a killed suspension of H. ducreyi. The skin test is performed by injecting 0.1 cc. of antigen intradermally. Seven millimeters of induration is considered a positive reaction. The test becomes positive ten to fifteen days after the appearance of the lesion[4]. Permanent skin sensitization results from a single attack of chancroid.

Seventy-one patients who showed lesions compatible with chancroid were found to have a positive skin test. The most common coexistent disease was syphilis. Only 10 cases of chancroid as a single entity were found. The remaining patients had coexistent venereal diseases and, as in lymphogranuloma venereum, it was impossible to say with certainty whether the genital lesions were due to the coexistent disease or to chancroid.

*Fusospirochetosis*

Primary fusospirochetosis may occur on the genitalia, causing lesions which simulate the venereal diseases. Fusospirochetosis also occurs as a secondary invader in genital lesions of other etiology. In only 2 of our cases did it occur as a primary disease. It was found in 20 patients examined for it, and occurred most often as a complication of granuloma inguinale. The diagnosis was made by finding the Spirillum and fusiform bacillus in spreads of the exudate stained with Wright's stain.

*Summary*

An analysis of the 3,701 admissions to the Rapid Treatment Center in Durham during the first seventeen months of its operation is presented. The incidence of occurrence and methods of diagnosis of the various venereal diseases are discussed.

# THUMBNAIL SKETCHES OF EMINENT PHYSICIANS

JOSIAH C. TRENT, M.D., F.A.C.S., *Editor*

ANN ARBOR, MICHIGAN

## THE STORY OF YELLOW FEVER

## II

## EIGHTEENTH-CENTURY PHYSICIANS AND THE YELLOW FEVER

Conveyed along trade routes from the tropical regions of America and Africa to the ports of the temperate zone, yellow fever became, during the eighteenth century, a major medical problem. The cities of the American seaboard carried on an extensive commerce with the West Indies, sending their lumber, fish, flour, and corn, and receiving in exchange sugar, molasses, rum—and yellow fever. More than thirty times in the course of the century the disease appeared in the American colonies in epidemic form. The physicians of New York, Philadelphia, Baltimore, Boston, and Charleston found themselves as helpless in dealing with this unwelcome visitor as were their colleagues in the West Indies, where the yellow fever was endemic and threatened the life of every newcomer from a northern country. The nature of the disease became a matter for discussion and dispute, often warm, but not often as heated as that which occurred between two physicians of Kingston, Jamaica. Doctors Williams and Bennet of that town engaged in an argument as to whether yellow fever was an "inflammatory disease"; the argument culminated in a duel on De-

cember 29, 1750, in which both physicians were killed.

The causation of yellow fever provided eighteenth-century physicians with wide ground for speculation. Each reasoned from the circumstances under which he encountered the disease. Dr. Williams of Jamaica, seeing that it was usually northerners, not yet acclimatized, who took the disease, maintained that it derived from "a sudden Check to Perspiration, a Redundancy of Bile"; when Europeans and North Americans indulged excessively in cool drinks or exercised violently in the heat of the tropical sun, their "callous Pores," "rigid Fibres and thick Blood" would not permit "an Evaporation equal to the effervescence raised within."[1] A Spanish physician insisted that an epidemic in Cadiz resulted from the eating of fruit and drinking of snow water. Some doctors in the American colonies, observing that yellow fever usually appeared or was most severe in coastal towns, originating in the overcrowded tenement areas near the filth of the wharves or in small and dirty ships, inclined to believe that the disease was generated by dirt and filth. Others suspected that the contagion was introduced by particular cargoes brought into port: slaves, timber, sugar, coffee, or coal. The prevalent tendency to confuse the yellow fever with malaria led still other doctors to contend that it was caused by miasmas arising from soil and damp, or from decomposing vegetable matter.

The difficulty of correctly diagnosing yellow fever—a difficulty not to be surmounted until the development of the serological tests of the present century—led to confusion of the disease with typhus, influenza, dengue, even scurvy, and frequently, as has been said, with malaria. In the nosologies of which eighteenth-century doctors were so fond, yellow fever and malaria were often represented as being only different degrees of autumnal fever: thus, yellow fever was said to be a severe and malignant manifestation of a contagion which appeared in milder form as remittent or intermittent fever. Errors in diagnosis sometimes arose from wishful thinking. Physicians were reluctant to recognize and proclaim the existence of yellow fever in their districts because the resulting panic and quarantine restrictions would utterly disrupt the whole life and commerce of the city. Such was the case in New York City in 1795, when Dr. Samuel Bard, then in his eightieth year, aroused the indignation of his colleagues and of the public by his persistence in declaring that yellow fever was present in the city; he held steadily to his purpose, however, until precautions had been taken to prevent the spread of the disease.

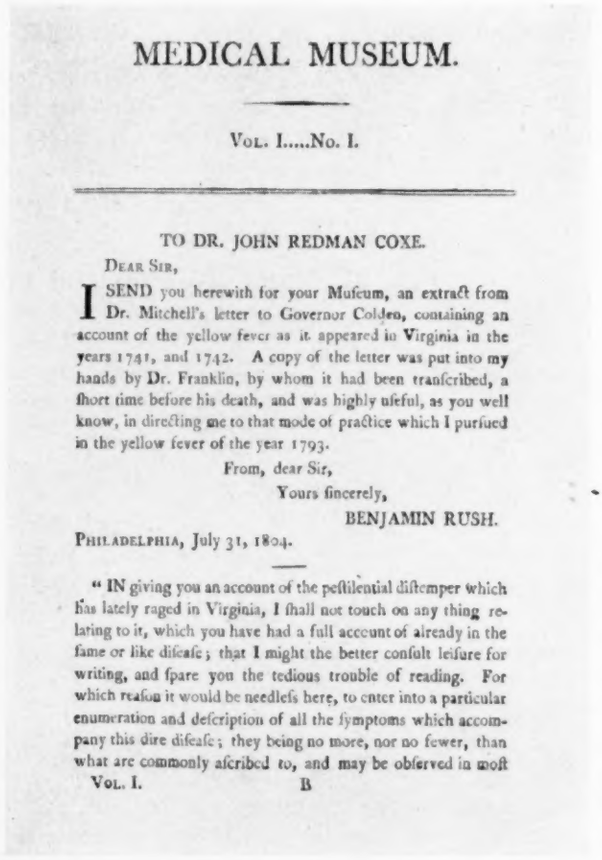
Facing the ravages of yellow fever in epidemic form, these eighteenth-century doctors found other work than speculation and theorizing. The prevention and cure of the malady became their immediate concern, and they made valiant, though futile, efforts to accomplish both. In practice as in theory, however, no common basis could be found, and the adherents of one method of treatment vehemently abused all others. It would be to small purpose to describe here the many and various remedies and prophylactics for the yellow fever which were proposed and tested, or the weighty arguments, couched in the defunct terms of humoral pathology, which were brought forward in defense of each remedy. The alexipharmac method—sweating followed by purging—was a favorite with many physicians; others preferred a reversal of this technique—mild purgation followed by natural sweating. Dr. John Mitchell, who practised in Urbanna, Virginia, from 1735 to 1746, was among the first to employ the latter method, and it may be of some interest to indicate briefly how he arrived at it. Mitchell observed the course of three yellow fever epidemics, in 1737, 1741, and 1742, and performed autopsies on the bodies of several slaves who died of the fever. He described the disease as a contagious inflammatory fever, caused by a venomous miasma received from without, which first assailed the abdominal viscera and caused mortification of those parts. Therefore he advised against the use of harsh medicines or sudorifics, which would aggravate the inflammation; bleeding would occasion "no less fatal dissolution of the fluids, or mortal debility." Instead, to accomplish the necessary evacuation of the poison and the "redundant Humours," he used mild purges to discharge from the viscera "their feculent corruptible contents."

> "By this evacuation likewise, great part of the offensive over-abounding minera of this disease proceeding from the putrid miasma, fermenting with the salivary, bilious and other inquiline humours of the body, is sometimes eradicated by timely emptying the abdominal viscera on which

1. Williams, John: An Essay on the Bilious, or Yellow Fever of Jamaica, Kingston, 1750, p. 17.

it first fixes; after the discharge of which a gentle sweat, does, as it were, nip it in the bud."(2)

Dr. Mitchell recorded his observations on the yellow fever and his provisions for its cure in several letters addressed to Dr. Benjamin Franklin and Governor Cadwallader Colden. One of these letters came to the hands of Dr. Benjamin Rush, who published it in the *Philadelphia Medical Museum,* in 1805 (fig. 1). Mitchell's argument found favor with Rush, who, as will be seen in the third sketch of this series, became the principal champion of treatment by a sterner sort of evacuation.



MEDICAL MUSEUM.

VOL. I.....No. I.

TO DR. JOHN REDMAN COXE.

DEAR SIR,

I SEND you herewith for your Muſeum, an extract from Dr. Mitchell's letter to Governor Colden, containing an account of the yellow fever as it appeared in Virginia in the years 1741, and 1742. A copy of the letter was put into my hands by Dr. Franklin, by whom it had been tranſcribed, a ſhort time before his death, and was highly uſeful, as you well know, in directing me to that mode of practice which I purſued in the yellow fever of the year 1793.

From, dear Sir,

Yours ſincerely,

BENJAMIN RUSH.

PHILADELPHIA, July 31, 1804.

" IN giving you an account of the peſtilential diſtemper which has lately raged in Virginia, I ſhall not touch on any thing relating to it, which you have had a full account of already in the ſame or like diſeaſe; that I might the better conſult leiſure for writing, and ſpare you the tedious trouble of reading. For which reaſon it would be needleſs here, to enter into a particular enumeration and deſcription of all the ſymptoms which accompany this dire diſeaſe; they being no more, nor no fewer, than what are commonly aſcribed to, and may be obſerved in moſt

VOL. I. B

**Fig. 1. The first page of a letter from Dr. John Mitchell to Cadwallader Colden on the yellow fever, published by Dr. Benjamin Rush in the Philadelphia Medical Museum for 1805.**

Although these eighteenth-century physicians labored vainly to combat or control yellow fever, they did compile a vast quantity of clinical and epidemiologic evidence on the disease—evidence marred by their confusion of yellow fever with malarial fevers, but sufficient to substantiate a few general statements. They discerned the reaction of the disease to climatic changes and were able to predict that epidemics would end with the coming of frost. They learned that flight from an infected area was the one sure prophylactic that they, with their knowledge of the disease, could prescribe. In tropical areas it was ascertained that only newcomers took the yellow fever, and doctors came to believe that acclimatization or a single attack of the fever conferred immunity. Dr. Henry Warren, in 1738, recognized that the black vomit characteristic of the fever in its most fatal form is actually blood and not the "black Bile or Choler." Dr. John Mitchell and others who sought knowledge of the disease by postmortem examination pointed out the characteristic hepatic lesion. Small gains, these, for more than a century's labor! The succeeding century, however, was to accomplish little more in solving the enigma of yellow fever.

J. C. T.

2. Mitchell, John: Account of the Yellow Fever in Virginia, in 1741 and 1742, Philadelphia Medical Museum, 1:13, 1805.

**Note:** Anyone desiring reprints of the first and second series of "Thumbnail Sketches" may obtain them by writing to Dr. J. C. Trent, 2108 Copley Avenue, Ann Arbor, Michigan.

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**Excessive dietary restrictions.** — The starvation treatments so popular amongst certain classes of educated persons, and the exaggerated notions entertained by them of the nutritive and health-giving properties of fruit juices and salads as a substitute for food, are not rarely followed in elderly atheromatous subjects by a rapid fall of blood pressure, marked fatigue, and the occurrence of cerebral thrombosis. What this semi-starvation does not achieve unaided in the way of disaster, a commonly associated addiction to saline aperients may bring about.

If these foolish practices are commonly indulged in at the behest of "healers" with no medical training, it can scarcely be denied that the ground has been long prepared for them by the dismal forebodings sometimes uttered to the subjects of high blood pressure by their duly qualified medical advisers, and by the excessive dietary and other restrictions imposed by them. Therefore when a patient seeks advice for symptoms associated with, and probably caused by, a developing cerebral atheroma, such, for example, as dizziness, headache, or undue fatigue, it is well to remember that there are limits beyond which it is not justifiable to interfere with his life. If he be habitually gross in his feeding and drinking, if he works to excess or takes some form of exercise unsuited to his condition, these habits must be corrected. On the other hand, it can rarely be necessary to forbid all meat and alcohol to such an individual. More often than not the patient's regime of life is a moderate and reasonable one, and in these circumstances only minimal restrictions should be imposed. The repeated taking of blood pressure readings may make the patient miserable and does not benefit the course of his malady.—F.M.R. Walshe, Diseases of the Nervous System, ed. 2, Baltimore, Williams and Wilkins, 1941, p. 94.

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FEBRUARY, 1946


## SERVICE TO SERVICE MEN

The Executive Committee of the Medical Society of the State of North Carolina met in Raleigh on Sunday, January 27. The minutes of the meeting will be published in the next issue of the NORTH CAROLINA MEDICAL JOURNAL, but it is not amiss to say now that in the course of this meeting the needs of the veterans, both laymen and doctors, who are returning to civilian life were given thoughtful consideration. A committee headed by Dr. E. McG. Hedgpeth recommended that the society cooperate with the Veterans Administration in offering medical service to veterans. The recommendation was unanimously adopted, and North Carolina is a close second to Michigan in sponsoring a plan whereby discharged service men can be treated in their own communities by their private physicians or by such specialists as are needed. The treatment may be given in the patient's home, in a hospital, or in the doctor's office, and the fees will be paid through the Veterans Administration. The Hospital Saving Association has been designated to administer the program when it is given final approval.

Much of Secretary McMillan's report was devoted to a discussion of ways whereby the returning medical officers might be aided in resuming their places in civilian practice. Most of his recommendations will be acted on by the House of Delegates at its meeting in May. One service which the Society can offer immediately, however, is the use of its official publication, the NORTH CAROLINA MEDICAL JOURNAL, as a medium for medical veterans to advertise their wants and needs. Any member of the State Society who is still in service or has recently been discharged and who would like to place an advertisement in the JOURNAL is asked to see the announcement on page 83.

* * * *

## BETTER MEDICAL CARE FOR *VETERANS*

The address of Major General Paul R. Hawley, acting surgeon general of the Veterans Administration, to the House of Delegates of the American Medical Association[1] will encourage those interested in the welfare of the veterans of both world wars. No one in his right mind will deny that there was need for radical reform in the Veterans Administration facilities, and General Hawley frankly admits that he and General Bradley are tackling "the greatest single problem that has ever faced American medicine." He further states that "The problem can be solved only by the organized medical profession of this country."

In reading the address one can hardly fail to be impressed with General Hawley's sincerity and with his desire to have the cooperation of the medical profession. He recognizes that the greatest mistake made by the Veterans Administration under its former management was in submerging "the medical service . . . under lay administrators —both in the central office in Washington and in the field." Another error which he acknowledges is that the Civil Service dictated the selection of new doctors. "They also prevented the removal of the poor material that did get in."

A third mistake pointed out by General Hawley has been the location of most Veterans Administration hospitals "in isolated places . . . by political expediency." In the future he proposes to build all Veterans Ad-

ministration hospitals where they can be associated with schools of medicine, or in towns which have a superior medical profession, so that it will be possible "to staff them almost exclusively by physicians in the private practice of medicine." Out-patient service to veterans is also to be rendered by private practitioners, so far as possible.

"In conclusion," said General Hawley, "I want to assure you that, even though I have spent thirty years in a highly organized government service of medicine, I should deeply regret a government control of the medical profession . . . I am just as interested as you are in keeping the government out of the medical business . . . If I am not permitted to bring the best in American medicine to the veteran, I shall withdraw at once from the program. I shall neither let down the veteran nor betray our own great profession."

1. *J.A.M.A. 129:1192-4 (Dec. 22) 1945.*

* * * *

## A SECTION ON GENERAL PRACTICE FOR THE AMERICAN MEDICAL ASSOCIATION

After two trial "Sessions for the General Practitioner" had been held under the auspices of the Section on Miscellaneous Topics, the Council on Scientific Assembly recommended to the House of Delegates of the American Medical Association at its December meeting in Chicago that "a proper amendment to the By-Laws be made to include a new section to be known as the section on General Practice." This recommendation was approved by the House of Delegates.

The new section should be of special interest to North Carolina doctors, since—so far as can be learned—our state medical society was the first to have a Section on General Practice. This section was created at the 1937 meeting, and has more than held its own in attendance at every subsequent meeting. Following North Carolina's lead, New York's Westchester County Society, the Connecticut State Medical Society, and the Southern Medical Association formed sections for the general practitioner.

The A.M.A.'s official adoption of its foundling section is a recognition of the general practitioner's important place in medical practice. Let us hope that the new section will continue to grow in usefulness.

## DO DOCTORS WANT TO LIVE ON TIPS?

In a recent debate on state medicine, a proponent of government control cited Sweden's system as a successful example. Since other advocates of federal medicine have also held up the Swedish plan as one to be emulated, it is well to know more about it.

In the second volume of Miss Esther Everett Lape's "American Medicine"[1] is to be found an account of state medicine in Sweden, written by a "Chicago pediatrician who was graduated from a Swedish medical school before coming to the United States." From this account we learn that "The country is divided into districts, each in charge of a physician who is a state official and receives a salary from the state . . . He has the right to charge only a small fee which is set by the state . . . He is entitled, however, to accept whatever fee is offered to him, and it is . . . not unusual for a patient to pay more than the minimum fee." If the doctor does well, he may eventually be promoted to the staff of one of the central hospitals owned by the state. Here "there are no professional charges, not even for major operations on private patients, but these latter are furnished with a list, compiled by the Swedish Medical Association, in which *suitable fees, scaled according to the patient's income, are suggested for various operations. It is quite unusual,* I have been told, *that the private patient does not follow these suggestions.*" (Italics ours)

If the meaning of the above words is as clear as it seems to be, the doctors of Sweden live largely on tips. It requires no great stretch of the imagination to conceive that a helpful nurse or house officer might, for a consideration, increase the size of the doctor's tip by suggesting ever so tactfully to the patient or to a member of his family that the surgeon's hand would be steadier if a suitable fee were paid in advance than if he were kept in doubt until the operation was over.

Somehow it is hard to think of an American doctor's putting himself in the position of a hotel waiter or bell-hop—even though he were made the head waiter of the Waldorf.

1. *American Medicine: Expert Testimony out of Court*, New York, The American Foundation, 1937, vol. 2, pp. 973-975.

## FUNDAMENTAL PRINCIPLES OF THE BRITISH MEDICAL PROFESSION

Although Great Britain has had a modified form of government medicine for many years (the "panel system"), the British medical profession is now faced with a proposed national health service that bears rather close resemblance to the system which Messrs. Wagner, Murray and Dingell are attempting to foist on this country. The similarity was explained by an article in the November issue of *Medical Economics*[1] which showed how such legislation originated in the International Labour Organisation. The *British Medical Journal* for December 15 gave first place to a statement of principles agreed upon by a Negotiating Committee "composed of representatives of the British Medical Association, the Royal College of Physicians of London, the Royal College of Surgeons of England, the Royal College of Obstetricians and Gynaecologists, the Royal Scottish Medical Corporations, the Society of Medical Officers of Health, and the Medical Women's Federation."

The statement is so clear and so brief that it is reproduced in full as evidence that British and American medical men see virtually eye to eye.

"For a quarter of a century the medical profession has stressed the need for a complete health service.

"The profession is willing and anxious to co-operate with the Government in evolving this service, for it believes that the knowledge and experience of the profession are indispensable contributions to its success.

"It re-emphasizes that good housing and social, economic, and environmental circumstances are the principal factors in the maintenance of health and the prevention of disease. It urges the expansion of medical research.

"In the interests both of the public and of medicine the profession regards the acceptance of the following principles as essential:

"I. The medical profession is, in the public interest, opposed to any form of service which leads directly or indirectly to the profession as a whole becoming full-time salaried servants of the State or local authorities.

"II. The medical profession should remain free to exercise the art and science of medicine according to its traditions, standards, and knowledge, the individual doctor retaining full responsibility for the care of the patient, and freedom of judgment, action, speech, and publication, without interference in his professional work.

"III. The citizen should be free to choose or change his or her family doctor, to choose, in consultation with his family doctor, the hospital at which he should be treated, and free to decide whether he avails himself of the public service or obtains independently the medical service he needs.

"IV. Doctors should, like other workers, be free to choose the form, place, and type of work they prefer without Governmental or other direction.

"V. Every registered medical practitioner should be entitled as a right to participate in the public service.

"VI. The hospital service should be planned over natural hospital areas centred on universities in order that these centres of education and research may influence the whole service.

"VII. There should be adequate representation of the medical profession on all administrative bodies associated with the new service in order that doctors may make their contributions to the efficiency of the service."

1. Labor's Program to Socialize Medicine Internationally, Medical Economics 23:36 (Nov.) 1945.

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## DR. ISAAC HALL MANNING

Just as the JOURNAL was going to press, news came that Dr. Isaac H. Manning had passed away, six weeks after he suffered a coronary thrombosis. The time is too short and the editorial space too limited to do justice to this great man. It is not a mere figure of speech to say that he was a medical statesman, and that his influence will live on and on, not only in North Carolina, but throughout the nation. The hundreds of students whom he taught during the forty years he was connected with the School of Medicine of the University of North Carolina are better men and better doctors for having known him.

The medical profession of the state and nation, and the public at large, owe him a deep debt of gratitude for the vision he had during his term as president of the State Medical Society—a vision of prepaid hospital care which became a reality in the Hospital Saving Association, the first Blue Cross plan to be sponsored by a state medical society. The confidence which the doctors of North Carolina had in Dr. Manning's integrity and ability made possible the accomplishment of his idea, and the success of North Carolina's program encouraged other states to undertake similar plans. Time alone will tell of the tremendous amount of good which will result from Dr. Manning's creative idealism.

His life was gentle; and the elements
So mixed in him that Nature might stand up
And say to all the world, "This was a man!"

# CASE REPORTS

## CLINICO-PATHOLOGICAL CONFERENCE

### BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

This 59-year-old cotton-mill worker entered the hospital on May 9, 1945, complaining of soreness and aching in the abdomen of three days' duration. The patient was so ill that it was impossible to obtain a satisfactory history. His illness began suddenly on May 7 at 1 a.m., when he awoke with a severe aching pain in the epigastrium and just below the umbilicus. This pain radiated from the right upper quadrant around to the right side, but the patient could not describe the exact location. The pain continued without remission until the patient was admitted to the hospital. He had also had some pain in the top of the right shoulder, but had had no nausea, vomiting, or chills. There had been a questionable weight loss of 15 pounds in the last three months. During the same period of time, the patient had noted a marked increase in urinary frequency and burning on urination.

For the past forty years the patient had had similar episodes of pain and chills at intervals of one to two years. These attacks always occurred at night, and never lasted more than an hour. He had never vomited. On a few occasions in the past he had noted light-colored stools and a few tarry stools. He said that on several occasions following the attacks of pain he had noted slight jaundice. At the age of 8 or 10 years he had been jaundiced, but he did not remember the details of his illness.

Two months before admission, the patient had a cold, which persisted and was associated with a dry, hacking cough. This was non-productive until the day of entry, when he coughed up 3 to 4 tablespoonfuls of thick, dark material. He had had some exertional dyspnea in the past and had awakened in the night with a sensation of smothering, so that he had to get up to get his breath. Slight ankle edema had been noted at the end of the day. There was a long history of urinary frequency and burning on urination. A kidney stone was passed twenty-five years previously.

The family history revealed that his mother died of consumption at the age of 50 years. His maternal grandmother had cancer of the eye, and his grandfather had had cancer of the nose.

*Physical examination*: The temperature was 102 F., pulse 105, respiration 24, blood pressure 120 systolic, 70 diastolic. The patient was a well developed and well nourished white male who appeared acutely ill. The skin was warm and moist. The heart was not enlarged and the rhythm was regular except for occasional extrasystoles. Moist rales were heard in both lung bases, more pronounced on the right side. There was tenderness to percussion in the right upper quadrant of the abdomen, the point of maximum tenderness being just beneath the middle of the right costal margin. There was some muscle-guarding over this area, but no definite mass was made out. Slight tenderness was noted in the right costovertebral angle and in both lower quadrants.

*Accessory clinical findings*: The urine had a specific gravity of 1.015 and a 4 plus reaction for albumin. Microscopic examination showed 6 to 10 coarse granular casts per high power field, 20 to 30 white blood cells, 65 to 85 red blood cells, and occasional white blood cell clumps; the urine was loaded with bacteria. The hemoglobin was 11.9 Gm., the red blood cell count 3,900,000, and the white blood cell count 14,600, with 76 per cent segmented polymorphonuclears, 12 per cent nonsegmented polymorphonuclears, 9 per cent small lymphocytes, and 3 per cent monocytes. The nonprotein nitrogen on May 10 was 55 mg. per 100 cc. of blood; on May 11, 94 mg. The carbon dioxide combining power on May 10 was 22 milli-equivalents per liter; on May 11, 20.3 milli-equivalents per liter. The blood chlorides were 90 milli-equivalents per liter on May 10 and 84 milli-equivalents on May 11. The icterus index was 100 units on May 11. An x-ray of the chest made on May 9 revealed "peculiar, diffuse, granular densities scattered throughout all the lung margins in both lung fields with generalized increase in vascular marking, but no localized areas of consolidation. The heart was within normal limits." A second chest x-ray on May 11 showed the picture unchanged. "There was no evidence of free air in the peritoneal space and the diaphragm appeared normal."

*Course in hospital*: Therapy consisted of glucose and saline intravenously, sulfadiazine, and digitalis. The morning after ad-

mission the patient's breathing was labored, and more moist rales were heard in both lung bases. He was placed in an oxygen tent. On May 11 he showed definite jaundice, and his condition was rapidly becoming worse; he was quite dyspneic. The temperature varied between 98 and 102.4 F., and the pulse ranged between 80 and 140. His abdomen became distended, but there was no rigidity. Multiple small, purplish petechiae ranging from 0.5 to 1 mm. in diameter appeared on the skin, scattered irregularly over the upper abdomen. The patient died rather suddenly on May 13.

*Discussion*

DR. GEORGE T. HARRELL: In summary, this is the story of a 59-year-old white male cotton-mill worker who died suddenly following an acute illness of seven days' duration, characterized by evidence of acute liver necrosis. The family history of tuberculosis in the mother and malignancy in two grandparents is significant. The patient's past history suggests involvement of the gastro-intestinal, respiratory, genito-urinary, and circulatory systems; it is characterized also by generalized symptoms which are somewhat non-specific. Since many symptoms of this present illness are referable to abnormalities noted in the past history, these will be discussed together by systems.

The weight loss of 15 pounds over a three-month period suggests that the present illness was preceded by a gradual downhill course. The finding of moderate degrees of fever with tachycardia suggests an infectious process, though the accessory data give no hint as to etiology or location. The past history of exertional and nocturnal dyspnea and ankle edema suggests a long-standing cardiac involvement, but the essentially normal blood pressure and the normal size of the heart point away from this. Extrasystoles were heard, however, and dyspnea did persist.

The possibility that the dyspnea might be on a respiratory basis is suggested by his exposure to cotton dust, although this rarely, if ever, leads to pulmonary fibrosis. A persistent respiratory infection accompanied by a dry cough had been present for two months, and on the day of admission he raised approximately 1½ ounces of thick, dark sputum. His respirations were constantly increased in rate; rales were noted at the base of the lungs, particularly on the right, but were not a striking feature. Scattered granular densities were noted in the x-ray, but no definite diagnosis can be made from the description.

At the age of 34 the patient passed a kidney stone, and frequency and burning of urination had persisted since that time. The right costovertebral angle tenderness noted on physical examination suggests that this chronic process was still active. The massive albuminuria and the increase in red and white blood cells and casts in the urine suggest also a very active process, with ulceration in the kidney and marked tubular involvement. The rising nonprotein nitrogen is indicative of increasing impairment of function. The type of organism responsible for the urinary infection is not identified, although it was seen in the urine sediment.

The predominant symptoms are referable to the gastro-intestinal tract. The history begins with jaundice at the age of 8 and continues with recurrent attacks of pain and chills since the age of 19, followed by slight jaundice and occasional evidence in the stool of blockage of bile. The acute episode of seven days' duration started suddenly with epigastric pain and pain in the right upper quadrant, the side, and the shoulder, continuing without remission for three days. The pain in the shoulder was undoubtedly referred from the dome of the diaphragm. Physical examination showed tenderness in the right upper quadrant, localized beneath the middle of the costal margin. The muscle-guarding over this area suggests acute inflammation. The tenderness in the costovertebral angle may have been referred from the kidney or from the posterior aspect of the liver. The tenderness in the right and left lower quadrants suggests some irritation of the peritoneum. The absence of air above the diaphragm and the presence of diaphragmatic irritation would tend to rule out perforation of a hollow viscus. The rising nonprotein nitrogen indicates that the liver was still able to deaminize protein, although there was sufficient destruction of liver tissue to produce jaundice and an icterus index of 100. The progressive distention without rigidity indicates paralytic ileus.

How can one tie all these findings together *etiologically*? The acute lesion in the lung suggested by the sudden expectoration of purulent material and by the x-ray findings might have occurred by direct extension through the diaphragm from the liver, as in

an abscess, or by extension from a lesion beneath the liver, as with peritoneal irritation from cholecystitis. The lesion may have followed invasion of the blood stream by the organism, or invasion of the lymphatics and entrance of the organism into the venous return. The sudden onset suggests a vascular accident or perforation of a hollow viscus; the sudden death suggests a similar accident. The appearance of purpura indicates a generalized involvement of blood vessels by the infectious process, or deficient prothrombin formation resulting from necrosis of the liver. Miliary tuberculosis might cause generalized scattered granular densities in the lungs, with purpura, peritoneal involvement, and massive involvement of the liver and kidney. The necrosis of the liver, however, is more marked than is usual with this disease. Metastasis from a malignancy may give these findings in the lungs and liver. The primary site would probably have to be in the gallbladder or liver, though bronchogenic carcinoma might cause the same picture. The repeated attacks of jaundice with light or tarry stools suggest recurrent passage of gallstones, with slight upper intestinal bleeding and occasional attacks of reflex spasm of the sphincter of Oddi. Some regurgitation of bile into the pancreas almost inevitably results from the recurrent passage of gallstones. This may lead to sudden edema and necrosis in the pancreas, with subsequent fibrosis and recovery, or with rapid progression to death.

It is always desirable to make a single diagnosis account for all findings, but I am unable to do so in this case.

*Dr. Harrell's Diagnoses*

1. Chronic cholecystitis with stones.
2. Spasm of the sphincter of Oddi.
3. Chronic pancreatitis, secondary, recurrent.
4. Acute necrosis of the liver with hypoprothrombinemia and purpura.
5. Terminal cerebral hemorrhage.
6. Acute and chronic pyelonephritis and cystitis.
7. Chronic non-inflammatory dust reaction in the lungs.

*Anatomic Discussion*

DR. W. C. THOMAS: The postmortem examination disclosed numerous petechiae and ecchymoses in the skin, lungs, heart, stomach, colon, kidneys, liver, and urinary bladder. The liver weighed 2,000 Gm. and was of a yellowish brown color. The kidneys weighed 225 Gm. and were a pale yellow-gray in color. Microscopic examination of the liver and kidneys showed marked cloudy swelling and small hemorrhagic areas. Sections of the liver, kidneys, and myocardium in Levaditi preparations showed numerous spirochetes which resembled those of the leptospira group.

This case presumably represents a fatal type of Weil's disease. It is unfortunate that the living spirochetes were not studied. Experienced observers of this form of the disease, however, have viewed these sections and confirmed our findings. We have seen 2 other fatal cases of the disease at autopsy. As far as I can ascertain, the disease has not previously been found on postmortem examination in North Carolina. It is hoped that these findings will stimulate clinicians in this part of the country to consider the possibility of Weil's disease in patients who present clinical symptoms compatible with this disease.

*Anatomic Diagnosis*

Leptospirochetosis ictero-hemorrhagica (Weil's disease).

*Closing Discussion*

DR. HARRELL: The final illness appears to have begun suddenly and progressed steadily. The gradual weight loss preceding the acute onset was misinterpreted as the beginning of the illness. The long history of gastro-intestinal and genito-urinary symptoms remains unexplained. Leptospirosis is an acute infectious disease and is rarely chronic or recurrent; hence the repeated bouts of jaundice could not be ascribed to that cause. Pre-existing liver damage may have made the final episode more fulminating in character.

There are two immunologic types of leptospira, for which rats and dogs serve as reservoirs. The organisms are excreted in the urine and the infection is usually found in men who work in wet places contaminated with urine of the carrier animals—sewer workers, miners, fish packers, and the like. No history of occupational exposure or of exposure from a pet dog was given in this case.

In the belief that cases of Weil's disease

were going unrecognized, Dr. O. T. Davis and I studied sera of all patients admitted to the North Carolina Baptist Hospital for several months during 1944, but were unable to detect the presence of lysins or agglutinins in several hundred specimens. The disease must be relatively rare.

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## CASE REPORTS FROM THE TUMOR CLINIC

### North Carolina Baptist Hospital

*Case 12*

C. B. L., a 9-year-old girl, was admitted to the surgical service of this hospital on January 10, 1946, with the following history. When the child was 18 months old, her mother noticed a lemon-sized mass in the left pectoral fold. She consulted her local physician, who kept the patient under observation for three months. The tumor was then removed in another hospital on March 7, 1938. A diagnosis of sarcoma was made from the pathologic study of this tissue. Shortly thereafter the patient's case was reviewed in still another hospital, where the operative site was irradiated. Following this therapy, the child remained well, gained weight, and developed normally. Several x-ray examinations of the chest, the last one made in August, 1938, were reported entirely negative.

Her present illness began on December 13, 1945, with an attack of influenza. Her symptoms, which were at first those of an upper respiratory infection, became exaggerated; her white cell count was elevated, and x-rays revealed two areas of increased density in the right lung field. The larger of the two was an orange-sized shadow at the level of the hilus; the smaller was lateral and inferior to the larger one. A diagnosis of pneumonia was made and penicillin therapy was instituted. The patient's acute symptoms subsided, though she continued to run a low-grade fever and the x-ray findings in her chest remained unchanged. She was referred to this hospital for further study and treatment.

On physical examination, the temperature was 99.2 F., the pulse 94, respiration 18, blood pressure 110 systolic, 75 diastolic. The patient was a well developed and normally nourished 9-year-old female who did not appear acutely ill. An oblique, well healed scar 4 cm. long was located in the left pectoral region. There were several slightly enlarged, non-tender, freely movable lymph nodes in both axillas, in the groins, and in the anterior cervical chains. The tonsils were slightly enlarged and chronically inflamed. Otherwise, the physical examination was completely negative.

Fig. 1

Three urinalyses were made. Aside from the demonstration of a trace of albumin and sugar on one occasion, and the persistence of a moderate number of white cells per high power field, no abnormalities were noted. The blood count showed 12.1 Gm. of hemoglobin, 4,150,000 red blood cells, and 6200 white blood cells. The corrected sedimentation rate was 11 mm. per hour. The serum proteins were 6.4 Gm. per 100 cc.

X-rays of her chest made on January 11, 1946 (fig. 1), were reported as follows: "The films of the chest showed two rounded, circumscribed lesions in the right lung field, one adjacent to the hilar shadow and a second smaller one in the peripheral portion of the right lower lobe just above the diaphragm. The lesions have the characteristic appearance of metastatic pulmonary infiltration."

*Tumor Clinic Discussion*

ROENTGENOLOGIST: Comparison of these films with the one taken December 17, 1945, shows a definite diminution in the size of the larger opacity. The fact that the opacity is smooth in outline, however, is not suggestive of pneumonitis. We feel that this patient has a metastasizing tumor.

PATHOLOGIST: We have here the original slides studied in 1938. Though I notice that the pathologist then believed this to be a metastasizing hemangioma or possibly a sarcoma of vascular origin, I am more inclined to think that it is a sarcoma arising from the nerve sheath (neurosarcoma). Numerous definite spindle cells are present, and there is no question that this is a malignant tumor.

SURGEON: We are at a loss to know exactly what to do with this patient. I am very strongly inclined to do a thoracotomy and try to remove the bulk of the tumor. The very fact that she has done so well for seven years following the removal of this tumor, with postoperative x-ray treatment, suggests that the same management would be advisable this time. It is, of course, extremely discouraging to operate on a metastasizing tumor, since one is always behind the process. We know, however, that a hypernephroma which has metastasized to the pulmonary field and lymph nodes can be controlled for several years by removal of the metastatic foci. If we can allow this girl four to five more years, I think we will be justified in operating. The position of this tumor, which will eventually result in blockage of her right lower lobe bronchus, with resulting atelectasis and sepsis, is another indication for removing it now. To attempt an operation after this process occurs would certainly be more risky. The child's family is very anxious to have the operation performed now. They were told at the time of the original operation that the child would probably not live more than two to three years, and she has done remarkably well for seven years. Therefore, they feel that repeating the procedure would be a definite advantage to the patient.

PEDIATRICIAN: Since this child is having no obstructive symptoms, and since the mass is now definitely smaller than on the previous film made in December, would it not be wise to postpone operation for a period of several months, having serial x-ray plates made to demonstrate changes in the size of the mass?

SURGEON: The ideal time to operate on any pulmonary tumor is before the advent of tracheobronchial obstruction. For that reason, I am inclined to advise operation before the patient gets into difficulty. I also believe that postoperative irradiation should be given, as it was following the previous operation.

*Tumor Clinic Opinion*

*Recommendation*: Exploratory thoracotomy with attempt at removal of the tumor masses.

*Prognosis*: Poor

*Blame*: Type of tumor.

*Follow-Up Note*

On January 14, 1946, exploratory thoracotomy was performed. It was found that both tumor masses were limited to the right lower lobe, and no metastatic lesions could be demonstrated in the mediastinum or pleurae. The right lower lobe was removed. The patient's convalescence has been satisfactory.

Microscopically the sections of the large nodule were made up almost entirely of necrotic and degenerated tissue filled with hemorrhage. Scattered through it were islets and strands of rather compact cells which had anaplastic characteristics and which for the most part were spindle-shaped. Some of the vessels in this degenerated tissue showed the same type of anaplastic spindle cells, which appeared to be attached to the endothelial surface and to be arranged in irregular groups or clumps. Sections of the smaller tumor mass showed a more cellular tissue composed of the same anaplastic spindle-shaped cells and round cells varying very little in size. The pathologic diagnosis was: "Fibrosarcoma, probably arising from the nerve sheath. Comment: Some may classify this tumor as a variety of endothelioma and conceivably it could be classified as a mesothelioma."

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**Diagnostic Fog.** It has been said that, if we know three important things that are really true about a disease condition, we are probably good diagnosticians; if we know five, we still may be good diagnosticians; but if we know too many things, mostly unimportant, and not all facts, we fail to distinguish the two-cent pieces of diagnostic material from the twenty-dollar gold pieces of fact, and we are likely to be lost in a diagnostic fog of our own creating.—William J. Mayo.

# MEDICOLEGAL ABSTRACT

J. F. OWEN, M.D., LL.B.
*RALEIGH*

*EVIDENCE: No person shall be compelled in any criminal case to be a witness against himself* (U. S. Constitution, Fifth Amendment).

The defendant in this case was charged with first degree murder. The record showed that on September 17, 1940, he fired three shots at his wife as she was fleeing from him, crying for help. There was evidence tending to show that he had lain in wait for her. After the third shot was fired, the victim did not speak again. At the hospital to which she was immediately taken, she was pronounced dead upon arrival. The evidence introduced in superior court showed a clear case of murder in the first degree, and the jury's verdict that the defendant was guilty of murder in the first degree made mandatory a sentence of death.

The defendant through his attorney appealed the case to the Supreme Court, noting three exceptions. The one of interest to the medical profession had to do with the introduction of certain evidence elicited by examination of the defendant's blood and urine. It was alleged that the defendant was forced to furnish the specimens for examination to determine the presence or absence of alcohol or morphine in his system. The defendant contended, therefore, that he was compelled to give evidence against himself in violation of the Constitutional inhibition against compulsory self-incrimination. The record, however, failed to show that the accused was forced against his will to furnish the specimens of blood and urine. This being the main question in issue as to this exception, the court did not sustain the defendant's allegation that he had been forced to provide the blood and urine for examination. The justice who wrote the opinion stated that it was a rule in the jurisdiction of the trial court that facts furnished by witnesses may be given in evidence, even where knowledge of such facts is obtained from the defendant in a privileged manner. Declarations of the accused obtained by improper influence, however, are to be excluded.

The judgment of the superior court was affirmed.

Many cases of a similar nature are coming up before the courts at present, especially cases which involve charges of driving while under the influence of alcohol. Scientific tests are now available to determine the exact amount of alcohol in a person's system by examination of expired air, blood, or urine. The courts thus far have been adverse to allowing such evidence to be introduced, because in the majority of instances the specimens of blood or urine have to be obtained by compulsive methods. Air tests, of course, may be done with a machine placed in the room or cell without physical contact, but there is still the element of forcing the defendant to give self-incriminating testimony. Despite the helpfulness and accuracy of such tests, it is doubtful whether the Constitutional provision prohibiting the obtainment of self-incriminating testimony by compulsion can ever be evaded. Another question which arises in this connection is who would be the proper person to give permission for the tests in the event that the accused was profoundly intoxicated and not able to do so himself.

At the 1945 session of the North Carolina Legislature, a law was passed providing a compulsive method for obtaining blood specimens from the mother and child in bastardy proceedings, the expense to be borne by the putative father. This method of determining paternity on the basis of blood types is by exclusion, but in certain cases positively rules out the possibility that the accused is the father of the child. This law, at first glance, would appear to be contrary to the Constitutional amendment regarding self-incriminating evidence, but in this case the mother and child are not charged with crime. (V. 15 S. E. Reporter 2nd. p 278. North Carolina Supreme Court, spring term, 1941)

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**The Social Handicap of an Irritable Bowel.** Many young women and some men with a sore colon are handicapped socially because whenever they go out to dinner or to a theater or dance, their excitement causes them to fill with gas. This rumbles and causes embarrassment as well as physical distress, and sometimes it causes them to go frequently to the toilet. Such persons can get much relief by taking a teaspoonful of paregoric or ½ grain of codeine sulfate before leaving home. These drugs apparently quiet the nerves to the bowel. Codeine has such an extremely small tendency to produce habituation that, specially when taken occasionally in this way, I see no reason for being afraid of it.—Alvarez, Walter C.: Nervousness, Indigestion, and Pain, New York, Paul B. Hoeber, Inc., 1943, p. 327.

# TUBERCULOSIS ABSTRACTS

*A Review for Physicians*

ISSUED MONTHLY BY THE NATIONAL TUBERCULOSIS ASSOCIATION

VOL. XIX FEBRUARY, 1946 No. 2


THE *Fourteenth Annual Report* of the Tuberculosis Committee of the American Student Health Association records the success of measures to control tuberculosis practiced by progressive institutions of learning in all parts of the country. The results must not be measured solely by the number of cases discovered. In the age group concerned this will always be small as compared to the general population. The search for cases, however, affords a unique opportunity for health education of both faculty and students. The practical demonstration of how to prevent tuberculosis will influence habits of thought and action long after text-book lessons are forgotten. This should make for closer cooperation between patient and physician the country over.

## TUBERCULOSIS AMONG COLLEGE STUDENTS

During the past three years there have been many factors which have interfered with the normal functioning of college health services. Yet the number of institutions having to discontinue their tuberculosis programs has been less than was anticipated. The Committee is confident that as our college enrollments return to normal and adequate medical personnel becomes available, we shall witness substantial progress in college health activities.

Many colleges are now planning for expansion which will provide more adequate health programs. The need for these may be better understood from the fact that less than half of the 886 colleges queried replied at all and of the 886 less than a third had tuberculosis programs. It may be safely assumed that those colleges which did not reply were without effective health programs.

The enrollment at colleges conducting case-finding programs in 1942-43 was 406,626. They reported 522 newly discovered cases of tuberculosis, a rate of 128 cases per 100,000 enrolled students. During the past school year, student enrollment at those institutions having survey programs was 286,018. Yet 622 new cases of tuberculosis were diagnosed, a rate of 217 per 100,000. This represents an increase of 19 per cent in the number of new cases of tuberculosis found in a student population which was 30 per cent below that of the previous year and reflects considerable improvement in the effectiveness of case-finding procedures. Of the 622 cases of tuberculosis diagnosed during the year at those colleges having case-finding programs, the lesions were classified as unstable in 156, quiescent in 151 and 315 were designated as healed. At many institutions the original tuberculosis program was frequently limited to entering students, whereas in recent years it has been expanded to include the entire student body.

There are now 93 universities and colleges which are conducting what may be considered practically ideal programs of tuberculosis control. Seventy-four colleges do routine tuberculin testing and X-ray all positive reactors each school year. Nineteen colleges report that chest X-rays are provided for all students annually, they having dispensed with preliminary testing. The programs of both groups of colleges offer a high degree of protection to their students. Cases of advanced tuberculosis among students at these 93 institutions should be encountered very rarely indeed, with such close supervision.

Reports were received from 114 colleges which do not sponsor any type of tuberculosis program. Student enrollment at these institutions was 121,133. There were 14 students found to have tuberculosis, a rate of 12 per 100,000. On the basis of this year's experience, therefore, colleges with case-finding programs diagnosed 18 cases of tuberculosis for each case diagnosed at those schools having no program. Such evidence should leave no doubt as to the wisdom of employing modern case-finding methods in every college.

The Committee again believes it advisable

to emphasize the need for active treatment in the majority of cases of tuberculosis found among young men and women of college age. Of the 622 new cases of tuberculosis among students 73 per cent of all new cases diagnosed during the year were permitted to remain in college. A considerable proportion of this group may experience progression of their disease and will eventually have to undergo treatment. Considerable time may elapse between the development of a new, unstable tuberculous lesion and the appearance of symptoms. Certainly every student who is found to have tuberculosis of recent development should be given the advantage of early treatment. Only when the lesion is judged to be stable and fibrotic is it justifiable to postpone treatment pending a period of observation.

The college which is attempting to protect its students against tuberculosis should give some thought to the possible dangers of non-student contacts. During the year there were 59 cases of tuberculosis diagnosed among faculty members and other employees and 18 cases among food handlers. Since the number of food handlers employed by a college is relatively small in comparison with the student enrollment, no great expense is involved in providing annual chest X-rays for this group.

The Committee believes there is ample evidence to justify the following statements relative to case-finding procedures commonly employed among college students:

1. The incidence of tuberculous infection among college students is steadily decreasing. The majority of reports from colleges in 1943-44 indicate infection rates varying between 15 and 30 per cent.

2. The two-dose Mantoux method is recommended as the method of choice for tuberculin testing. If a single test dose is employed, an intermediate dose of at least 0.1 mg. O.T., or 0.0001 mg. P.P.D. should be used. The Vollmer patch test cannot be recommended for use in colleges.

3. The Mantoux test is highly dependable in eliciting sensitivity due to significant tuberculous infection or disease. It is sound practice, and in the interests of economy, to provide chest roentgenograms for only those students who react to an adequate dose of tuberculin.

4. Complete protection against tuberculosis for college students cannot be attained through a program limited to the student body. Faculty members and employees, including food handlers, should participate in the tuberculosis control program on the same basis as students.

5. The lesions of pulmonary tuberculosis encountered in college students are, in a majority of instances, unstable and potentially dangerous. The absence of symptoms does not preclude the necessity for early treatment. Students who remain in college having pulmonary lesions, should be under close observation with frequent clinical and roentgenographic studies.

*Tuberculosis Among College Students, H. D. Lees, M.D., The Journal-Lancet, September, 1945.*

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# CORRESPONDENCE

January 25, 1946

To the Editor
NORTH CAROLINA MEDICAL JOURNAL

Dear Sir:

The following is a brief report concerning an outbreak of psittacosis in a group of parakeets that came into North Carolina several weeks ago. It is felt that this report might be of interest to the physicians of the state.

Following the 1930 outbreak of psittacosis in this country the United States Public Health Service initiated a system of control of interstate shipments of psittacine birds. Such birds must be quarantined for two weeks before shipment to another state, the receiving state being notified when the shipment is made. Under this system local health officers in North Carolina have been inspecting incoming birds.

On November 7, 1945, two local health officers notified this office that dead or sick birds had been found in shipments reaching Wilson and New Bern. A check-up revealed that these birds were part of a single lot that had been distributed among stores in eight additional North Carolina towns and cities. Health officers at these points were notified to destroy the birds and to send the carcasses to the National Institute of Health for examination.

Laboratory work was done on fourteen parakeets and two canaries from five localities. A total of eight parakeets were found infected with psittacosis. The canaries, also

a part of one infected shipment, were negative.

The incubation period for the human contacts has elapsed without any known instances of infection.

In view of the increase in intercontinental travel and a corresponding risk in the importation of infected birds into this country, North Carolina's recent experience may be a warning of future difficulties.

In the 1930 outbreak approximately 170 human cases of psittacosis occurred in the United States. Of these, 19 per cent died. Since that time approximately 200 more have been reported, with a 21 per cent fatality rate. Recent United States reports are as follows: 1942, 32 cases; 1943, 2; 1944, 6; and in 1945 (first nine months), 12 cases.

At its December meeting, the State Board of Health considered ways and means of tightening the present North Carolina restrictions governing psittacine birds. The problem is complicated by the fact that the psittacosis virus has recently been shown to be only one of several related agents capable of producing virus pneumonia, among them being ornithosis, spread by pigeons.

The Attorney General is now studying the extent of the authority under which the North Carolina State Board of Health might prohibit all incoming shipments of psittacine birds. However, the entire subject of bird-borne disease remains to be explored, and the control of psittacosis may, in the future, become only one part of an overall program to control diseases spread by birds.

Yours sincerely,

CARL V. REYNOLDS, M.D.
Secretary and State Health Officer.

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The age-old war between man and the tubercle bacillus has killed more people than all the wars between nations. After centuries of bondage to this killer, man has begun to free himself in recent years. Although certain biologic and economic factors may have aided, medical science has at least provided control devices which are effective against his enemy. He is in retreat, but not yet conquered. In fact, he threatens a successful counter-attack through conditions imposed by war and economic disturbance. This attack is aimed toward industry. We can contain the enemy and again throw him back if we concentrate our fullest forces in industry. The mass x-ray method of finding cases is our new rocket gun. This is the time and place to use it. W. P. Shepard, M.D., Rocky Mountain Med. Jour., June, 1944.

# BULLETIN BOARD

## NOTICE TO RETURNING MEDICAL OFFICERS

The business manager of the NORTH CAROLINA MEDICAL JOURNAL has authorized the JOURNAL to open its columns to returning medical officers who wish to advertise for a location, an office, a home, or equipment. Any member of the State Society who is in service or has recently been discharged from service may insert without charge such a notice of fifty words or less. The advertisements should be typed in double space and mailed to the NORTH CAROLINA MEDICAL JOURNAL, 300 S. Hawthorne Road, Winston-Salem 7, N. C., before the twenty-fifth day of the month preceding publication. Each advertisement will be inserted only one time unless notice is given for renewal in the next month's issue.

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### STATE BOARD OF MEDICAL EXAMINERS

The State Board of Medical Examiners will meet in Raleigh at the Woman's Club, 314 Hillsboro Road, March 25 to 28, inclusive, to give examinations to candidates for licensure. Candidates for reciprocity licenses will be interviewed on March 26.

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### STATE MEDICAL CARE COMMISSION

Dr. W. T. Sanger of Richmond, president of the Medical College of Virginia, was elected president of the special committee recently chosen by the State Medical Care Commission to make a survey of hospital facilities and medical education in the state and to select a site for the expanded medical school and hospital of the University of North Carolina.

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### NEWS NOTES FROM THE STATE BOARD OF HEALTH

In 1939, the North Carolina diphtheria case rate was approximately three times that for the United States, while in 1944-1945, our rate was approximately twice that for the nation as a whole.

It was in 1939 that the state-wide immunization law was enacted. The next year showed a 50 per cent decline in our case rate. This probably was due, in large measure, to the sharp decline in the disease which occurred throughout the United States that year. In 1944, North Carolina had reduced its diphtheria case rate 75 per cent, as compared with 1939, while in the United States the rate had dropped 40 per cent for the same period.

In 1945 the North Carolina diphtheria case rate increased 129 per cent, as compared with the previous year, while the increase in the nation as a whole was only 39 per cent.

## News Notes from the University of North Carolina

Dr. George L. Carrington and Dr. R. E. Brooks, both of the class of 1918, of the Alamance General Hospital, Burlington, have given a grant-in-aid to establish a graduate fellowship at the University Medical School in the Department of Biological Chemistry and Nutrition for the purpose of studying the relationship between the oxalic acid content of foods, especially those of regional importance, and the formation of oxalate calculi.

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Dr. H. G. Baity, Professor of Sanitary Engineering of the School of Public Health, was in New York during the early part of January to attend the following meetings: Meeting of the Committee on Advancement of Sanitary Engineering of the American Society of Civil Engineers; the Annual Meeting of the American Society of Civil Engineers; and the meeting of the New York Sewage Works Association.

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Dr. M. J. Rosenau, Dean of the School of Public Health, attended meetings of the Executive Board of the American Public Health Association in New York January 24, 25, and 26. Dr. Rosenau will go to Puerto Rico during February, where he has been invited, as president-elect of The American Public Health Association, to give the address at the annual meetings of the Puerto Rico Public Health Association in San Juan, February 6 to 9.

## News Notes from the Bowman Gray School of Medicine of Wake Forest College

Dr. David Cayer, of the Department of Medicine, discussed "The Laboratory Diagnosis of Deficiency Diseases" before the twenty-fifth annual New Year's meeting of the Marlboro County Medical Society, held at Bennettsville, S. C., on January 10.

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Dr. Frank R. Lock, of the Department of Obstetrics and Gynecology, was guest speaker at the meeting of the Norfolk County Medical Society in Norfolk, Va., on January 14. His subject was "Postpartum Tubal Ligation—Indications." He also spoke in Greenville, S. C., on February 4, and discussed "Pregnancy and Endometriosis" at the meeting of the South Atlantic Association of Obstetricians and Gynecologists, held at Sedgefield on February 15.

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Dr. George Harrell, director of the Department of Medicine, addressed the Norfolk County Medical Society on February 11, on "Rickettsial Spotted Fever."

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Dr. Wingate M. Johnson of the Department of Medicine has gone to Chicago to attend the conference of secretaries and editors at A.M.A. headquarters on February 8 and 9, and to represent the school at the annual congress on medical education and licensure, February 10-12.

## News Notes from the North Carolina Tuberculosis Association

A mass meeting was held in the Chowan County Courthouse in Edenton on December 13 for the purpose of forming a county-wide tuberculosis association. After much discussion a motion was made and passed that the county form a tuberculosis association. A committee was then appointed to draw up a slate of officers and directors. Another meeting will be held soon to complete the organization.

## First District Medical Society

The meeting of the First District Medical Society was held on December 5 at the Hotel Joseph Hewes in Edenton. After a very delightful meal served in the dining hall, the meeting was called to order by the president, Dr. Cola Castellow of Windsor. The following officers were elected for 1946: president, Dr. Thomas L. Carter, Gatesville; vice president, Dr. J. Gaddy Matheson, Ahoskie; secretary-treasurer, Dr. R. H. Vaughan, Edenton.

Dr. Oren Moore, president of the State Medical Society, and Dr. Roscoe D. McMillan, secretary, spoke in the interest of organized medicine in North Carolina. Dr. J. Gaddy Matheson, councilor of the First District, was present and made brief remarks.

## Third District Medical Society

The Third District Medical Society held a dinner meeting in Clinton on January 15. Speakers on the program were Dr. Roscoe D. McMillan, secretary of the State Medical Society; Dr. Robert B. Lawson of the Bowman Gray School of Medicine of Wake Forest College; Dr. J. Warrick Thomas of the Vaughn Memorial Clinic, Richmond, Virginia; and Dr. Keith S. Grimson of the Duke University School of Medicine.

Officers elected for 1946 were Dr. W. S. Dosher of Wilmington, president, and Dr. Robert M. Fales of Wilmington, secretary and treasurer. Outgoing officers were Dr. O. L. Parker of Clinton, president; Dr. J. D. Robinson of Wallace, vice president; and Dr. D. M. Royal of Salemburg, secretary and treasurer.

## Alamance-Caswell Counties Medical Society

Dr. John E. Dees of the Duke University School of Medicine was guest speaker at the January meeting of the Alamance-Caswell Counties Medical Society, held in Burlington on January 8. His subject was "Office Management of Urological Problems."

## Cabarrus County Medical Society

Dr. Guy L. Whicker of Kannapolis has been elected president of the Cabarrus County Medical Society and chief of staff of the Cabarrus County Hospital for 1946, succeeding Dr. Julian Busby of Kannapolis as president of the society and Dr. R. B. Rankin of Concord as chief of staff. Other officers for 1946 are Dr. J. E. Nance of Kannapolis, vice president of the society and assistant chief of staff, and Dr. R. E. Moorefield, secretary-treasurer of both groups.

## Edgecombe-Nash Counties Medical Society

The January meeting of the Edgecombe-Nash Counties Medical Society was held in Rocky Mount on January 9. Dr. Robert Whitley discussed "Medical Emergencies" and Dr. Robert Kornegay gave a talk on "Indications for Paravertebral Block."

## Warren County Medical Society

Dr. H. H. Foster of Norlina was elected president of the Warren County Medical Society for 1946, succeeding Dr. T. J. Holt of Wise. Dr. G. H. Macon of Warrenton was elected vice-president and Dr. W. D. Rodgers secretary-treasurer. Dr. F. P. Hunter and Dr. C. H. Peete of Warrenton were chosen as delegates to the State Medical Society.

## Wilkes-Alleghany Counties Medical Society

The Wilkes-Alleghany Counties Medical Society has recently held two dinner meetings, to which doctors from Elkin were invited. Dr. J. H. McNeill of North Wilkesboro, recently returned to civilian practice, talked about the practice of medicine in the navy, and Dr. Felda Hightower of the Bowman Gray School of Medicine of Wake Forest College spoke on "Malignant Lesions of the Large Bowel." Officers of the Wilkes-Alleghany Counties Society for 1946 are Dr. F. C. Hubbard, president; Dr. J. H. McNeill, secretary-treasurer and delegate to the State Medical Society; and Dr. H. B. Smith, alternate delegate. The Society made a contribution to aid the work of the National Physicians Committee for the Extension of Medical Service.

## News Notes

Dr. Estus White of Kannapolis was elected man-of-the-year in the annual contest sponsored by the Kannapolis Junior Chamber of Commerce and **The Daily Independent.** Miss Louise Harkey, superintendent of Cabarrus County Hospital, was chosen woman-of-the-year.

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Dr. Russell S. Beam of Lumberton died suddenly in his office on January 9.

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Dr. Evan M. Hutchins of North Wilkesboro died in his sleep on October 30.

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Dr. John F. Williams, retired physician of Copeland, died in Elkin on January 9.

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Mrs. T. W. M. Long of Roanoke Rapids, widow of the late Dr. Tom Long, secretary of the State Medical Society from 1937 until his death in 1941, was killed instantly by an automobile on January 15, as she was crossing the street near her home.

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Dr. W. L. Taylor and Dr. Ballard Norwood, both of Oxford, were injured in a head-on collision of their automobiles on January 8.

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Dr. C. C. Orr of Asheville has resigned as councilor of the Tenth District Medical Society because of disability resulting from a coronary thrombosis which he suffered in November.

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Dr. Frank Edmondson of Tarboro has recently been discharged from the army and has gone to Asheboro to be associated with Dr. J. L. Fritz.

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Dr. Dennis Fox of Randleman has been made staff surgeon at the Yadkin Hospital in Albemarle following his discharge from the army after three and a half years of service.

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Dr. Franklin M. Grady, who was recently discharged from the army, has opened offices in New Bern for the general practice of medicine.

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Dr. William A. Farmer has joined the staff of the Highsmith Hospital in Fayetteville to do general surgery. Dr. Farmer was recently discharged from the army with the rank of major.

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Dr. Walter Kempner of the Duke University School of Medicine was guest speaker at the New York Academy of Medicine on January 15.

Dr. Joseph P. McCracken, who was discharged from the army with the rank of major after 44 months of service, has opened offices in Durham for the practice of internal medicine.

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Dr. James Mills of Henderson has gone to North Wilkesboro to practice medicine.

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Dr. William Smithie, who was recently discharged from the army, has joined the surgical staff of Park View Hospital in Rocky Mount.

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Dr. H. J. Bradley of Brevard is taking a refresher course at the Bowman Gray School of Medicine of Wake Forest College following his separation from the armed service.

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The following North Carolina doctors have recently been discharged from the armed forces and have returned to civilian practice:

Dr. John C. Burwell of Greensboro
Dr. E. W. Furgurson of Plymouth
Dr. Isaac E. Harris, Jr., of Durham
Dr. Will H. Lassiter of Selma
Dr. Lester P. Martin of Mocksville
Dr. W. H. Patton, Jr., of Morganton
Dr. J. Dan Redwine of Lexington
Dr. John G. Smith of Rocky Mount
Dr. James B. Woods, Jr., of Davidson

* * * *

Capt. Jesse B. Caldwell, Jr., of Cramerton, has been awarded the Bronze Star "for meritorious service in connection with military operations against an enemy of the United States in France, Belgium, Luxembourg and Germany from Nov. 6, 1944 to March 22, 1945."

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The Bronze Star was awarded to Major Richard F. Richie of Raleigh for meritorious service in military operations against the enemy from Dec. 13, 1944 to May 8, 1945 in the United Kingdom, France, Belgium and Germany.

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Capt. Gordon B. Tayloe of Aulander received the Legion of Merit "for exceptionally meritorious conduct in the performance of outstanding services to the government of the United States as senior medical officer of the United States Naval Group in China from Sept. 29, 1943 to June 5, 1945."

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The Legion of Merit has been awarded to Lieut. Col. Thomas H. Tomlinson, Jr., of Thomasville for developing and supervising the theater hospitalization program for a period of more than thirty-three months.

## ASTP Graduates to be Called to Active Duty

The War Department announced on January 9 that more than 5,000 young medical officers trained under the army specialized training program will be called to active duty July 1 to replace Medical Corps officers eligible for discharge. The ASTP will be discontinued on this date, and the 3300 men in this program who will receive their medical diplomas at that time will be called to active duty when their internships are completed. Members of the ASTP who have not completed their medical education on July 1 will be transferred to the Enlisted Reserve Corps.

# PHYSICIANS DISCHARGED FROM SERVICE

The following list of North Carolina doctors who have been discharged from service was obtained from the *Journal of the American Medical Association.* Additions or corrections should be sent to the editorial office, 300 S. Hawthorne Road, Winston-Salem 7, N. C.

Alexander, Leo., Major, Durham
Augustine, R. W., Capt., Gastonia
Barnes, Henry Eugene, Capt., Hickory
Benbow, John T., Major, Winston-Salem
Bennett, John W.
Benton, George R. J., Lt. Col., Goldsboro
Benton, Wayne J., Capt., Greensboro
Bland, Charles A., Major, Forest City
Bostic, William C. Jr., Capt., Forest City
Branning, William S., Capt., Durham
Brewton, William A., Lt. Col., Enka
Bridges, Dwight T., Capt., Lattimore
Brown, Ivan W. Jr., Capt., Durham
Burgess, Woodrow W., Major, Durham
Burwell, John C., Major, Greensboro
Byrd, Charles W., Capt., Bunnlevel
Calder, Duncan G. Jr., Major, Charlotte
Caldwell, Jesse B. Jr., Capt., Cramerton
Cannon, Edward G., Hope Mills
Cherry, James H., Major, Asheville
Clapp, Hubert L., Major, Swannanoa
Cleland, William A., Capt., Durham
Cornell, William S., Lt. Col., Charlotte
Covington, Furman P., Capt., Thomasville
Craven, Frederick T., Capt., Concord
Cree, Maurie B., Major, Concord
Croom, Robert D. Jr., Major, Maxton
Curtzwiler, Francis C., Lt. Col., Wilmington
Cutchin, Joseph H. Jr., Capt., Whitakers
Dougherty, John H., Major, Asheville
Elfmon, Samuel L., Capt., Fayetteville
Fales, Robert M., Capt., Wilmington
Farmer, William A., Major, Fayetteville
Felton, Robert L. Jr., Capt., Carthage
Fenner, Edwin F., Col., Henderson
Fleming, Lawrence E., Major, Charlotte
Floyd, Anderson G., Capt., Whiteville
Fox, Dennis B., Capt., Greensboro
Frazier, John W., Lt. Col., Salisbury
Gardner, Clarence E. Jr., Lt. Col., Durham
Gay, Charles H. Sr., Capt., Charlotte
Glenn, Eugene B., Capt., Asheville
Goldstein, J. J., Capt., Wilmington
Goswick, H. W. Jr., Capt., Winston-Salem
Griffis, John W., Capt., Denton
Haar, Frederick B., Greenville
Hall, Edgar M. Jr., Ist Lt., Raleigh
Hardin, Parker C., Monroe
Harney, James N., Capt., High Point
Harris, Isaac E. Jr., Lt. Col., Durham
Harris, Jerome S., Major, Durham
Hawes, George A., Capt., Charlotte
Hawes, James B., Capt., Greenville
Hawkins, William C., Major, Asheville
Helsabeck, Belmont A., Capt., Winston-Salem
Hill, Abel L., Capt., Kings Mountain
Holladay, Beverly L., Capt., Statesville
Horger, Eugene L.
Hunt, Walter S. Jr., Capt., Raleigh
Hunter, John F. C., Capt., Magnolia
Hutchinson, Robert H., Capt., Durham
James, William D., Capt., Hamlet
Johnson, Gaston F., Capt., Spray
Johnston, William O., Lt. Col., Charlotte
Jones, Otis H., Capt., Charlotte
Kennedy, Leon T., Major, Winston-Salem
Ketchie, James M., Capt., Salisbury
Killian, Frank M., Capt., Franklin
Kornegay, Robert D., Capt., Rocky Mount
Lancaster, Forrest J., Capt., Lexington
Lebauer, Maurice L., Major, Greensboro
Lewis, Walter G., Capt., Stokesdale
Lyon, Brockton, R., Lt. Col., Greensboro
McDonald, Lester B., Major, Hendersonville
McFadyen, Oscar L., 1st. Lt., Fayetteville
McGrath, Frank B., 1st Lt., Lumberton
McIntosh, Donald M., Jr., Major, Marion
McKee, Lewis M., Capt., Durham
Melcher, Willis A., Capt., Wilson
Melton, Harry R.
Meriwether, Ben M., Major, Asheville
Moore, Henry B., Major, Graham
Moorefield, Robert H., Capt., Kannapolis
Murphy, Gibbons W., Asheville
Newell, Hodge A., Henderson
Norton, J. W. R., Lt. Col., Chapel Hill
Odom, Robert T., Capt., Winston-Salem
Padgett, Philip G., Capt., Kings Mountain
Patterson, Fred G., Major, Chapel Hill
Perryman, Olin C., 1st. Lt., Winston-Salem
Persons, Elbert L., Lt. Col., Durham
Phelps, John M., Creswell
Pickard, H. M., 1st. Lt., Wilmington
Pillsbury, Henry C.
Pitts, William R., Major, Charlotte
Poole, Marvin B., Capt., Dunn
Pope, Samuel A., Capt., Beulaville
Powell, Eppie C., Major, Goldsboro
Reavis, Charles W., Major, Kinston
Renegar, James G., Capt., Southern Pines
Ring, Louis J., Lt. Col., Mt. Olive
Rhodes, James S. Jr., Capt., Williamston
Richie, Richard F., Major, Raleigh
Riley, Philander C.
Robertson, Lloyd H., Capt., Salisbury
Robinson, Robert L., Major, Mars Hill
Rowe, George C., 1st. Lt., Charlotte
Sader, Julius, Major, Brevard
Salle, George F., Capt., Vanceboro
Sanger, Paul W., Lt. Col. Charlotte
Sawyer, Logan E., Major, South Mills
Sinclair, Robey T. Jr., Major, Whiteville
Sirlin, Edward M., Lt. Col., Durham
Smith, Charles G., Capt., Rocky Mount
Smith, John G., Capt., Rocky Mount
Sotirion, George A., Capt., Charlotte
Sox, Carl C., Lt. Col., Kenly
Spencer, Thomas B., Capt., Charlotte
Stenhouse, Gordon C., Capt., Durham
Straughan, John W., Capt., Warsaw
Stroupe, Albertus U., Capt., Mt. Holly
Sykes, Joy V., Rocky Mount
Taylor, Edmund R., Capt., Chapel Hill
Thomas, Walter L., Major, Durham
Thomas, William C., Major, Siler City
Thurston, Thomas G., Capt., Rocky Mount
Tice, Walter T., Major, High Point
Tilton, Welcome B., Capt., West Asheville
Troutman, Baxter S., Capt., Lenoir
Tyndall, Robert G., Kinston
Tyson, Thomas D. Jr., Capt., Mebane
Warshauer, Samuel E., Major, Wilmington

**Physicians Discharged from Service—(Continued)**

Warwick, Hight C., Capt., Greensboro
Washburn, Chivous Y., Capt., Mooresboro
Wilson, James S., Capt., Kenansville
Wilson, Samuel A., Major, Lincolnton
Windley, William H., Major, Washington
Winstead, Maurice B., Major, Washington
Wisely, Martin R., Major, Edenton
Wood, Frank, Major, Marion
Wood, George T. Jr., Col., High Point
Worth. Thomas C., Major, Raleigh
Young, Joseph A., Major, Newton

## News Notes from the Office of the Surgeon General

**Further Criteria Reductions for MC, DC, and VC.**

Further criteria reductions to make additional doctors, dentists and veterinarians available for civilian practice were announced recently by Major General Norman T. Kirk, The Surgeon General of the Army.

While the number of professional men affected by this action will not be more than a thousand, The Surgeon General's Office has ordered this revision of criteria in line with the Medical Department's policy of doing everything possible to expedite the return of doctors, dentists, and veterinarians to private life.

The following specialists in scarce categories will be released with a critical score of 80, continuous service since Pearl Harbor, or if the age of 45 has been reached: Eye, ear, nose specialists; orthopedic surgeons; and internal medicine specialists. A requirement of 70 points, 45 months service, or 45 years of age limit will make the following eligible for separation: gastroenterologists, cardiologists, urologists, dermatologists, anaesthetists, psychiatrists, general surgeons, physical therapy officers, radiologists, and pathologists. Plastic surgeons will be eligible for release if they have a critical score of 80, or service since Pearl Harbor, or if they are 48 years of age.

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**General Lull Leaves SGO for AMA**

Major General George F. Lull, Deputy Surgeon General of the Army, whose notable record in that capacity won him the Distinguished Service Medal, the highest noncombatant award, has retired from the Army after 33 years of service with the Medical Corps. General and Mrs. Lull will move to Chicago where General Lull will become Secretary and General Manager of the American Medical Association. He will take up his new duties officially when the retirement of Dr. Olin West, the present Secretary and General Manager, becomes effective, but he will immediately join the staff of the American Medical Association to familiarize himself with the work of the organization.

Born in Pennsylvania March 10, 1887, General Lull received his M.D. degree from Jefferson Medical College in 1909, a Certificate of Public Health from Harvard Technology School of Public Health in 1921, and his degree of Doctor of Public Health from the University of Pennsylvania in 1922. He is an honor graduate of the 1913 class of the Army Medical School.

Brigadier General Raymond W. Bliss, Assistant Surgeon General and Chief of Operations Service, has been appointed Deputy Surgeon General to succeed Major General Lull.

**Refresher Training for Doctors Leaving Service**

Refresher training of twelve weeks' duration will be given Army doctors leaving the service who desire to brush up on latest developments in fields of medicine, surgery, or neuropsychiatry in which they may not have been actively practicing during the past year, Major General Norman T. Kirk, Surgeon General of the Army, announced recently.

This training, which will prepare retiring Army doctors for return to private practice with latest knowledge of medical advances made during the war, will be given at Army hospitals until June 30, 1946. Reserve Corps, National Guard, and AUS Medical Corps officers who are to be separated will be eligible for this schooling.

The election of the period of refresher training is entirely voluntary, and applications may be made through channels to The Surgeon General in the case of medical officers assigned to the Army Service Forces, Army Ground Forces and Army Air Forces. Medical officers returning from overseas may make application for refresher training from the Reception Stations or Separation Centers through the ASF Liaison Officer directly to The Surgeon General. It is pointed out that medical officers cannot be recalled to active duty from terminal leave for the purpose of accepting a professionl assignment for refresher training.

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**Danger of Malaria Epidemic Steadily Decreasing**

Risk of introduction of an epidemic of malaria by returning soldiers from overseas is continually decreasing, according to a statement by Major General Norman T. Kirk, Surgeon General of the Army. The situation is reflected in the rate of admissions of malarious cases in hospitals in this country which reached a peak of 6,000 cases in February of this year and has been following a declining curve since that time, General Kirk said. It is expected that the rate will continue to go down because a large proportion of the personnel of divisions heavily seeded with malaria in the early stages of the war already have been returned to this country.

## United Nations Relief and Rehabilitation Administration

Packaged as neatly as deliveries from a city department store, complete outfits for 28 hospitals, totalling more than 26,000 beds, are on the way to three stricken countries in Europe as result of efforts of special representatives of the United Nations Relief and Rehabilitation Administration, according to word received at the agency's Washington headquarters.

The hospital outfits, purchased from Army surpluses in the United Kingdom and on the European continent, are being trucked or shipped by sea to Poland, Czechoslovakia, and Yugoslavia.

Diseases resulting from malnutrition, exposure and filth have swept across Poland, Czechoslovakia and Yugoslavia. Tuberculosis and venereal infections have shown vast increases. The need for hospital facilities, according to reports by UNRRA missions and appeals from the European countries, is far greater than before the war began. But the hospitals which existed at that time were systematically looted by the Axis, and in many cases destroyed. Hence, the governments appealed to UNRRA for aid.

UNRRA will not supply buildings for the hospitals. The individual governments will furnish them, and the outfits furnished by UNRRA will transform them into operating institutions.

BULLETIN BOARD CONTINUED ON PAGE 91

# AUXILIARY

## WHY ARE YOU NOT AN AUXILIARY MEMBER?

Why are you not a member of the Auxiliary? Is it because there is no auxiliary in your county, because you are too busy with other organizations to belong to the Auxiliary, because of pressing home situations, or just because?

For a successful organization there must be enthusiasm and happiness. This is gained only through willing groups, and each one of us should be willing to learn the functions of the Auxiliary in order to serve the medical profession. The principal interests of the Auxiliary are: health education, public relations, legislation, philanthropy, and social functions. The most important objectives of an Auxiliary are to direct public thinking and actions in channels the medical profession desires, and to extend authentic information on health. We support an organization only when we belong to it and understand its tasks and objectives and how to accomplish them.

A busy wife is an asset to the Auxiliary if she is an informed member, because she has many opportunities to carry the aims and decisions of the medical profession to other organizations. It is not necessary to partake of every phase of the Auxiliary work to be a good member; each member should do only what she can, but do it well.

Our membership has dropped off in the past four years, but enthusiasm and determination to keep what we have established have not waned. The increased support of the county medical societies has not been a small factor in the growth of the Auxiliary. There is an urgent need to strengthen our present auxiliaries and to organize new ones if we are to continue to prove worthy of our name. It is not hard to organize. Write your councilor or organizing chairman for instructions.

Because you are a doctor's wife who understands the supreme unselfishness and the greatness of the profession, you should find the Auxiliary worth while. Join your local auxiliary. If your county does not have an auxiliary, help to organize one! If this is not possible, become a member-at-large. Join today and say, "I am a member of the Auxiliary."

*The Treasurer, Mrs. E. C. Judd, 2108* Woodland Avenue, Raleigh, will be glad to receive your dues.

MRS. J. T. SAUNDERS, Asheville
*Chairman of Organization.*

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## DOCTOR'S DAY, MARCH 30

Again we pay tribute to our doctors at home, and to those still engaged in the armed forces throughout the world. The public appreciates the burden that has been carried during the years of war by the physicians left at home. They responded to a call of duty no less urgent than that of the physician in uniform, and met the home front's redoubled demands with tireless devotion.

Physicians are returning daily to take their places in the various communities from which they were called. They are sincerely welcomed by the friends and acquaintances they once more meet. How good it must make the returning physician feel, when someone clasps his hand and says, "Thank goodness you're back, Doctor!"

On this Doctor's Day, 1946, let us also pay honor and respect to our gallant physicians who have made the supreme sacrifice. "Died in the line of duty" we read after each name. Undoubtedly each would have chosen to go this way.

We honor all of the physicians all over the world. Time means nothing to them as long as humanity can be served. May the year 1946 find the burden lighter for the older physicians, and open new and shining roads to the younger.

MRS. JOHN E. G. MCLAIN
Doctor's Day Chairman.

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## THE DOCTOR

Long years of costly study makes one fit
To treat the sick, to set the bones, to bind
Up wounds, to cure, alleviate disease.
Medicine is science, art, and not
A commodity. The service doctors give
Cannot be bought. It is a priceless gift.

BLANCHE C. HOWLETT

(from the *Journal of the American Medical Association*).

# BOOK REVIEWS

**Mitchell-Nelson Textbook of Pediatrics.** *Edited by Waldo E. Nelson, M.D., Professor of Pediatrics, Temple University School of Medicine. With the Collaboration of Forty-Nine Contributors. Ed. 4, revised. 1350 pages with 519 illustrations on 333 figures, 26 in color. Price, $10.00. Philadelphia and London: W. B. Saunders Company, 1945.*

As a textbook of pediatrics, this new edition of an old standard work cannot be too highly recommended to students, practitioners, and specialists. Dr. Nelson has done a magnificent job of assembling the best contributions from a number of well qualified authors into an easily read volume.

This is, in truth, an entirely new book; but the aim of presenting the characteristics, growth, and development of the normal child as well as those of the child affected by disease, has been adhered to as in the previous editions.

There are a number of new chapters; among them, those on congenital malformations and malignant tumors in early life are of special interest. Among the important and hitherto neglected subjects which are well discussed are the various psychopathologic disorders and problems of the adolescent. Each section is preceded by a general discussion and review of the normal physiology of that particular system; then the abnormal variations are discussed. There are numerous tables and graphic charts, and many excellent illustrations, some colored. Each section is concluded with an excellent and comprehensive bibliography.

The arrangement of the sections leaves little to be desired. The appendix is filled with a number of valuable tables of normal values.

If one were to be limited to only one volume on pediatrics, this reviewer would unhesitatingly recommend Dr. Nelson's comprehensive and well written book.

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***Virus as Organism.*** *By Frank M. Burnet, M.D., Director, Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne, Australia. Price, $2.00. 134 pages. Cambridge, Mass.: Harvard University Press, 1945.*

This delightful monograph attempts to strip away the aura of mystery which surrounds viruses. The author traces the possible evolution of viruses from simple structures and points out that their dissociation into variants follows the same biologic principles as those operating for bacteria. Considering the relative size of viruses and bacteria, our knowledge of viruses is surprisingly great rather than meager. The dependence of the virus on the host cell for nutrition and for enzymatic respiration leaves the small virus as "a shadowy, self-replicating residuum of genetic mechanism." The control of virus diseases in the future must depend on a knowledge of the method by which the virus survives, so that its life cycle can be interrupted. Various specific viruses are discussed.

This book is highly recommended as a readable, intriguing approach to the study of virus diseases.

**Textbook of Neuropathology.** *By Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School. Ed. 2. 370 pages. Price, $5.50. New York: Grune and Stratton, Inc., 1945.*

This book by Dr. Weil fills a great need for an English textbook of neuropathology, since all previous textbooks on this subject were in French or German. The outstanding features of this book are its conciseness, its clarity, and its inclusiveness. It deals with all the important disease processes which attack the central nervous system and are understood pathologically today. The contents are very well organized and the book is well indexed, so that any subject is easy to locate.

The chapter on "Anemic Softening" is especially commendable. The chapters dealing with degenerative disease of the nervous system and with tumors could be expanded and more amply illustrated. The appendix of the book is especially valuable. It deals with the techniques of fixation of the central nervous system tissues, and includes the various staining methods employed in neuropathology. This is a special type of technique, which is not given in many other textbooks. The bibliography of the book is adequate. The publishers are to be congratulated upon the paper and the binding.

This book will probably be of most value to medical students and house officers. They can gain from it a fundamental knowledge of the underlying pathological processes which give rise to disturbances in physiology. It would also be valuable for the average practitioner of medicine who wants to know something of the fundamental pathology of nervous diseases. For the man who deals comprehensively in nervous system disease, such as the neurologist, the neurosurgeon and the neuropathologist, however, more detailed information would be required.

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**Clinical Traumatic Surgery.** *By John J. Moorhead, B.S., M.D., D.Sc., F.A.C.S., (D.S.M.), Formerly Professor of Clinical Surgery, New York Post-Graduate Medical School, Columbia University, and Executive Officer, Department of Traumatic Surgery, Post-Graduate Hospital and Reconstruction Hospital Unit; Diplomate in Surgery; Colonel, Medical Corps (A.U.S.) Inac. Res.; Medical Director, New York City Transit System. 747 pages with 500 illustrations. Price, $10.00. Philadelphia and London: W. B. Saunders Company, 1945.*

In a clear, concise manner the author has thoroughly covered the field of traumatic surgery by eliminating old, outmoded procedures and verbose descriptions while including all the essentials in both chemotherapeutic and technical fields. The descriptions of recent procedures which have proved valuable tremendously enhance the value of the book. All types of injuries to different parts of the body have been discussed in necessary detail, but without unnecessary verbiage.

Both physicians and surgeons will find the book of value, since it deals not only with the diagnosis and treatment of injuries, but with the near and remote possible complications, including even traumatic neuroses. The compensation and medicolegal aspects of trauma are well covered. This volume will serve admirably for those dealing with industrial accidents, as well as for all general surgeons and even for the general practitioner, who not infrequently is called upon to render at least first aid care, which is so admirably covered in this text.

**The Care of the Neurosurgical Patient before, during, and after Operation.** By Ernest Sachs, M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri. 268 pages. Price, $6.00. St. Louis: The C. V. Mosby Company, 1945.

The author of this book is one of the older and more experienced neurological surgeons. As a manifestation of his interest in teaching younger men, he dedicated this book to his former Fellows in Neurosurgery.

There has been a great need for a book giving the details of preoperative and postoperative care of neurosurgical patients. One must remember, however, that there is a great need of individual variation in the preoperative and postoperative care of any patient; in the neurological patient this is especially true. Therefore many of the techniques and much of the equipment illustrated and discussed in this book differ from equipment and procedures employed elsewhere. In general, however, the book is a good "rough guide."

Much of the material in this book is a repetition of material contained in the author's previous book entitled **The Diagnosis and Treatment of Brain Tumors.** A disproportionate amount of space is given to operative methods and techniques for a book which is intended to deal with the care of the neurosurgical patient. The paper on which the book is printed is none too good in quality, but the binding is satisfactory and the material is fairly well indexed.

This book would be of especial value to the nursing staff of hospitals where neurosurgical patients are treated and would serve as a guide for house officers. It would also be of help to the general practitioner and to doctors in other specialties who see an occasional neurological emergency case. The book would be only an adjunct to the library of the well-trained neurosurgeon and neurologist.

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**Howell's Textbook of Physiology.** Edited by John F. Fulton, M.D., Sterling Professor of Physiology, Yale University School of Medicine. Ed. 15. 1304 pages with 507 illustrations. Price, $8.00. Philadelphia and London: W. B. Saunders Company, 1946.

This book is advertised as a fifteenth edition of Howell's **Textbook of Physiology.** However, it fully deserves to be called the first edition of Fulton's **Textbook of Physiology,** as it has been completely rewritten from cover to cover by some twenty contributors under Dr. Fulton's editorial direction. While a small number of applied topics are included, the book is intended primarily as an exposition of fundamental physiology, and as such, it excels any book at present available. The book is profusely illustrated throughout with new diagrams and reproductions of figures from recent physiological literature. The text is well written and follows a logical plan of organization. The table of contents is particularly useful, as it includes all section headings and occupies some twenty-seven pages of the text. The sections on muscle, nerve, the nervous system, the cardiovascular system, metabolism, and the endocrines are particularly well done. The book is highly recommended to all medical students and will be found useful for the physician interested in understanding the basic physiology of the human body.

**Physiology in Health and Disease.** By Carl J. Wiggers, M.D., D. Sc., F.A.C.P., Professor of Physiology, School of Medicine of Western Reserve University, Cleveland, Ohio. Ed. 4, thoroughly revised. 1174 pages, illustrated with 247 engravings. Price, $10.00. Philadelphia: Lea and Febiger, 1944.

This book has been thoroughly revised and brought up to date in almost all sections. It continues to maintain its high standard of excellence both as to basic fundamental physiology and as to the applications to clinical medicine. This edition has been recently reprinted and further corrections were made. The large number of references to the recent literature make this text particularly useful. This book is recommended both to the student of physiology and to the practitioner.

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**Treatment in General Practice.** By Harry Beckman, M.D., Professor of Pharmacology, Marquette University, School of Medicine, Milwaukee, Wisconsin. Fifth Edition, reset. 1070 pages, illustrated. Price, $10.00. Philadelphia and London: W. B. Saunders Company, 1945.

This standard work has apparently achieved wide success, since a new edition is required in three years. The arrangement follows that of Cecil's **Textbook of Medicine,** so that the two books can be used as companion volumes. Since it is designed in this fashion, the book would be much more usable if the long clinical descriptions were eliminated. The diagnosis of a case must be established before one looks up the therapy, and hence the lengthy discussions seem superfluous. The book suffers from lack of critical evaluation on types of therapy. The elimination of obsolete and obscure methods would help to shorten and improve the work.

The inclusion of prophylactic measures is an excellent contribution. The psychoneuroses, however —one of the greatest problems in practice—receive little attention. The author wisely stresses the fact that therapy must be individualized; yet in the discussion of the collapse therapy of tuberculosis, he recommends following the practice prevalent in the community. This inevitably would lead to the most conservative measures and would prevent the best possible treatment.

A complete and up-to-date bibliography is included.

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**Common Ailments of Man.** By Morris Fishbein, M.D., Editor of **Hygeia** and of the **Journal of the American Medical Association.** 177 pages. Price, $1.00. New York: The Garden City Publishing Company, 1945.

This little book discusses the following subjects: common colds and respiratory infections, backache, headache, hemorrhoids, sinusitis, allergy, arthritis or rheumatism, neuritis, varicose veins, anemia, nephritis, the prostate gland, heart disease, high and low blood pressure, athlete's foot, and constipation. Each chapter was written for **Hygeia** by a reputable doctor, and has been revised and brought up to date. The book is as free as possible from technical terms, and should be understood by any intelligent layman. None of the articles are calculated to alarm the reader nor to arouse false expectations of miraculous cures in hopeless conditions.

The work can safely be recommended to one's patients who may ask about it, with the assurance that there is nothing in it to shake the confidence of the patient in his doctor.

**Hematology for Students and Practitioners.** By Willis M. Fowler, M.D., New York: Paul B. Hoeber, Inc., 1945

This is a most satisfactory book. The format, typography and illustrations are a great credit to the art of book-making.

Of the contents one may say that they are worthy of the dress that the publishers have given them. All the hematological syndromes are clearly described, the clinical pictures as well as the hematological details. The modern viewpoints are everywhere well presented, and practical details in subjects like transfusion of blood are clearly presented. The chapter on hematological methods is full and helpful.

One defect should be mentioned. Too little attention is paid to the study of bone-marrow. This is one of the newer and more important fields of blood work and should be emphasized. Also, it would not be difficult to improve the bibliographies of the various subjects .

All in all, this seems to the reviewer to be among the very best works on hematology designed for students and practitioners that has appeared, and it can be enthusiastically recommended.

---

**Psychiatry in Modern Warfare.** By Edward A. Strecker, M.D., Litt.D., LL.D., Professor of Psychiatry, School of Medicine, University of Pennsylvania; Consultant for the Secretary of War to the Surgeon-General of the Army and the Army Air Forces; Consultant to the Surgeon-General of the Navy; Consultant to the Surgeon-General, U.S.P.H.S.; and Kenneth E. Appel, Ph.D., M.D., Sc.D., Assistant Professor of Psychiatry and Chief of Clinic, School of Medicine, University of Pennsylvania; Lecturer in Psychiatry, School of Neuropsychiatry, U. S. Naval Hospital, Philadelphia. 88 pages. Price, $1.50. New York: The Macmillan Company, 1945.

This little book by Drs. Strecker and Appel fills a much needed place in psychiatric literature at this time. The nation has become increasingly aware of the role of psychiatry in its military machine, and there has been a great deal written by psychiatrists, sociologists, psychologists, and pseudo-psychiatrists concerning the relationship of the nation to its psychiatric casualties. **Psychiatry in Modern Warfare** is a sane and authentic inquiry into this urgent national problem. The book is written in a manner which will make it useful not only to doctors, social workers, and other professional people, but also to intelligent laymen.

There is a detailed consideration of the method in which modern warfare has brought about an increased incidence of neurological and psychological disorders. The second section of the book deals with demobilization and the return of service men to civilian life. This section could be read with benefit by every American who is at present facing the problem of helping a returned service man to make the readjustment to civilian life. The authors are optimistic about the situation, but anticipate the need for clear-headed national thinking about this matter. They stress the need for more adequate veterans' hospitals and for more and better-trained psychiatrists and psychiatric personnel.

Altogether this book is to be heartily recommended.

***A Future for Preventive Medicine.*** *By* Edward J. Stieglitz, M.D. 73 pages. Price, *$1.00. New York: The Commonwealth Fund,* 1945.

This small monograph is one of a series on "Medicine and the Changing Order." The author stresses the increasing importance of degenerative diseases, and especially those associated with mental disturbances. The need for research on the etiology of endogenous degenerative diseases is stressed. The author recommends that periodic health inventories or surveys be done by practicing physicians; he terms this practice **constructive** rather than **preventive** medicine. The recognition of the medical profession's responsibility for health education, beginning with courses in biology in the secondary schools, is a healthy approach which should appeal to lay educators as well.

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# BULLETIN BOARD

(CONTINUED FROM PAGE 87)

## National Conference on Medical Service

The nineteenth annual meeting of the National Conference on Medical Service was held on February 10, 1946, in Chicago.

## American College of Surgeons

The American College of Surgeons announces the resumption in 1946 of its Sectional Meetings, which during the war were replaced by one-day War Sessions. Most of the Southern states, including North Carolina, were represented at a meeting held in the Tutwiler Hotel, Birmingham, on February 8 and 9.

## Vermont State Medical Society

The Vermont State Medical Society announces the opening of executive offices at 128 Merchants Row, Rutland, Vermont.

## Iowa State Medical Society

Effective January 1, 1946, Everett M. George, M.D., recently returned from service with the United States Navy, assumed the position of Editor of the **Journal of the Iowa State Medical Society**. Dr. George succeeded Lee Forrest Hill, M.D., who held that position for the past nine years.

## Institute for Vitamin Research

Robert Stanley Goodhart, M.D., since March 1943 chief of the Industrial Feeding Program Division, War Food Administration, Department of Agriculture, has been named Scientific Director of the Institute for Vitamin Research, Inc.

## New Potent Antimalarial Developed

Two young chemists in the Rensselaer, N. Y. laboratories of the Winthrop Chemical Company, Inc., made the original synthesis that formed the basis of "SN 7618", new potent antimalarial announced in Washington, D. C., by the Board for the Coordination of Malarial Research and described as relieving acute attacks of the disease "three times faster than Atabrine or quinine."

They are Dr. Alexander R. Surrey, 32, and Henry F. Hammer, 24. Their work was finished March 1, 1944, and the compound, labelled by Winthrop as WIN-244, was immediately turned over to the National Research Council for screening and clinical testing.

## Prize Contests

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons Foundation announces that the annual prize contest will be conducted again this year. For information address Dr. James R. Bloss, secretary, 418 Eleventh Street, Huntington 1, West Virginia.

* * * *

The American Urological Association offers an annual award 'not to exceed $500' for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the secretary for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Netherland Plaza, Cincinnati, Ohio, July 22-25, 1946.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before July 1, 1946.

* * * *

The National Gastroenterological Association announces the establishment of an Annual Cash Prize Award of $100 and a Certificate of Merit for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The winning contribution will be selected by a board of impartial judges and the award is to be made at the Annual Convention Banquet of the National Gastroenterological Association to be held at the Hotel Pennsylvania in New York City on Thursday evening, June 20, 1946.

Certificates awarded to other physicians will be mailed to them. The decision of the judges will be final. The Association reserves the exclusive right of first publishing the winning contribution, and those receiving certificates of merit, in its official publication, **The Review of Gastroenterology.** All entries for the 1946 prize should be limited to 5,000 words, be typewritten in English, prepared in manuscript form, submitted in five copies, accompanied by an entry letter, and must be received not later than May 1, 1946. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23, N. Y.

**Physician wanted** to serve as county physician and director of large venereal disease clinic. Salary $4000.00 to $4500.00 plus travel allowance. Address Business Manager, **North Carolina Medical Journal**, Red Springs, N. C.

**Wanted**—A competent physician interested in industrial medicine. To supervise the Medical Department of a 5,000 employee textile operation in North Carolina. The plant has a well equipped Medical Department and nursing staff. Plant practice only, five days per week (approximately 40 hours.) Address Business Manager, **North Carolina Medical Journal**, Red Springs, N. C.

### Rutin Ready for Commercial Production

The U. S. Department of Agriculture has announced that rutin, a drug with medical values undetected for more than a century, is ready for full scale production for the first time, and enough to meet present medical needs in treating fragile and weakened capillaries will be available this year.

Commercial manufacture of rutin, a bright yellow non-toxic powder, has been made possible by the discovery by the Bureau of Agricultural and Industrial Chemistry that the green buckwheat plant is an economical source. The search for a plant yielding rutin has been carried on at the Bureau's Eastern Regional Research Laboratory over the past two years, and the findings indicate that the need for rutin, including its likely use in human nutrition, may take as much as 10 per cent of the pre-war buckwheat acreage.

According to clinical observations at the Medical School of the University of Pennsylvania, rutin is effective in the treatment of conditions arising from high blood pressure associated with increased capillary fragility. Bursting of weakened blood vessels causes small hemorrhages which may result, when the rupture occurs in the eye or brain, in blindness or apoplexy.

Research indicates also that rutin, a glucoside, may have equally unsuspected nutritional values. Further investigation of the nutritional uses is expected, but the studies point to the opinion that rutin could serve the circulatory system in a manner resembling the action of vitamin C in the growth and hardness of teeth and bones.

---

### The A.P.A.A. (Ninth) 1947 Exhibition*

to be held at Atlantic City, on the occasion of the Centennial Session of the American Medical Association, will also be the occasion of the judging of the "Courage and Devotion Beyond the Call of Duty" Art Prize Contest ($34,000 in Savings Bonds).

This contest was originally scheduled for the 1946 A.M.A. Session but has been postponed one year, upon the best advice, in order to give more physicians an additional year to complete their art pieces on this special prize subject.

* For further information regarding both the San Francisco 1946 and the Atlantic City 1947 Art Exhibits, physicians may write either the American Physicians Art Association Secretary-Treasurer, Dr. Francis H. Redewill, Flood Building, San Francisco, Cal., or the sponsor, Mead Johnson & Co., Evansville 21, Ind.

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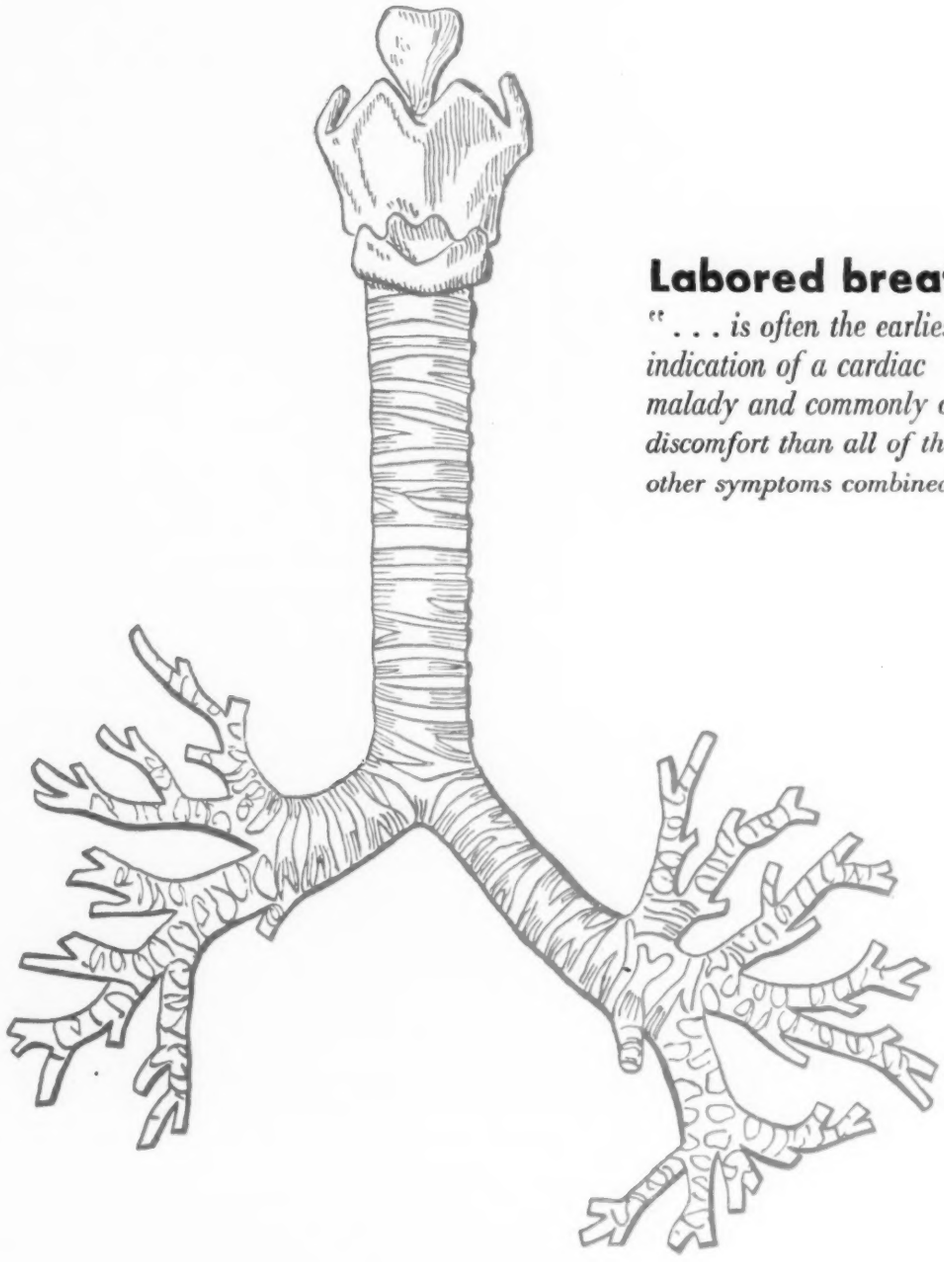

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*1. Harrison, T. R.: Cardiac Dyspnea, Western J. Surg., 52:407 (Oct.) 1944.*

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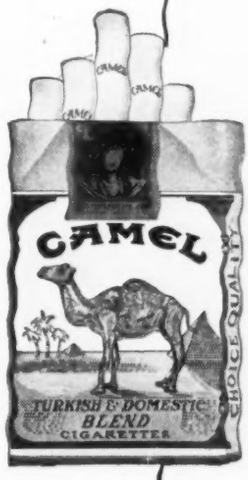


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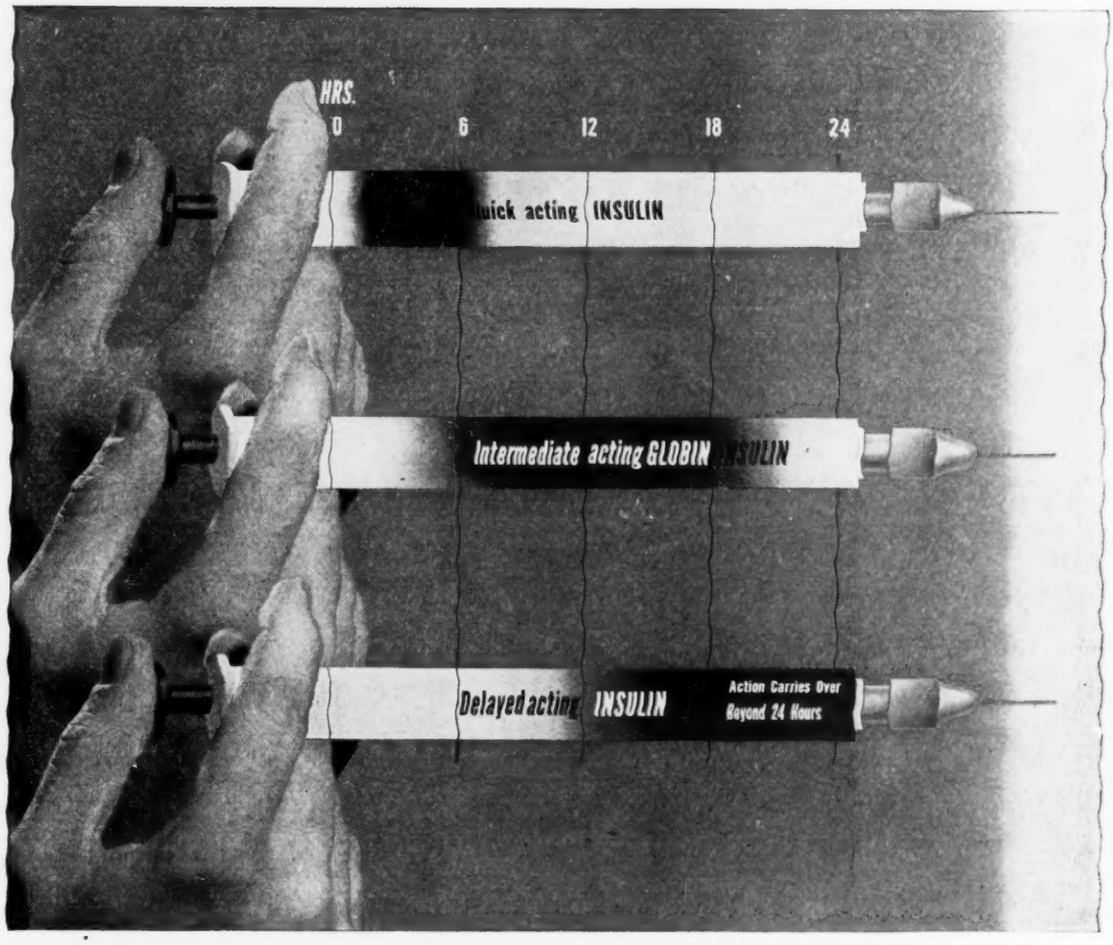


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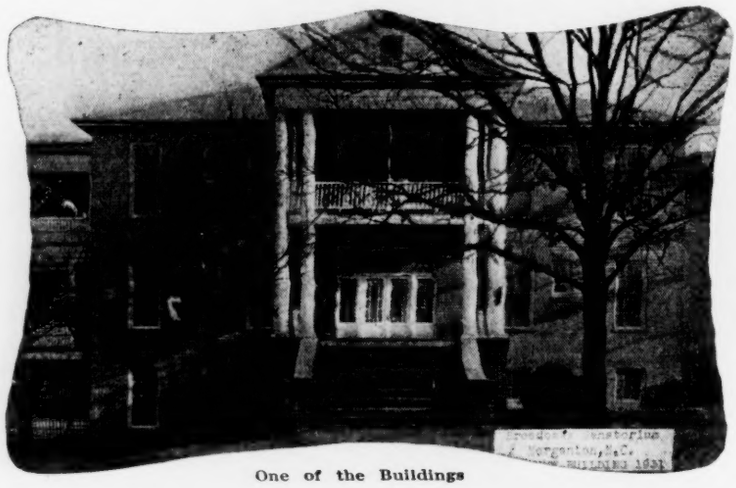

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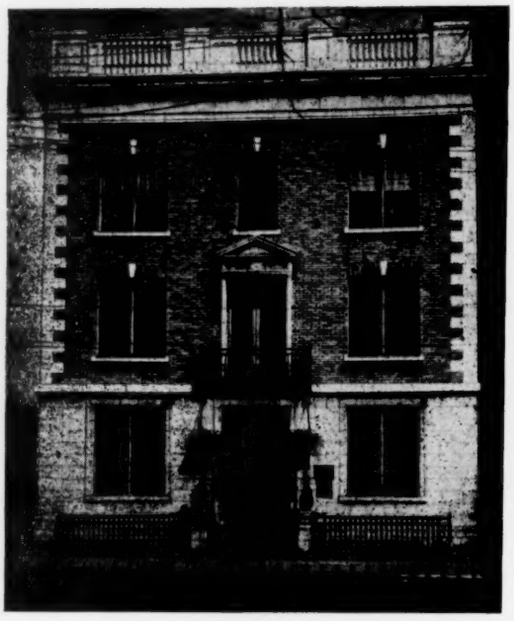

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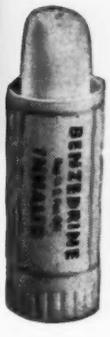


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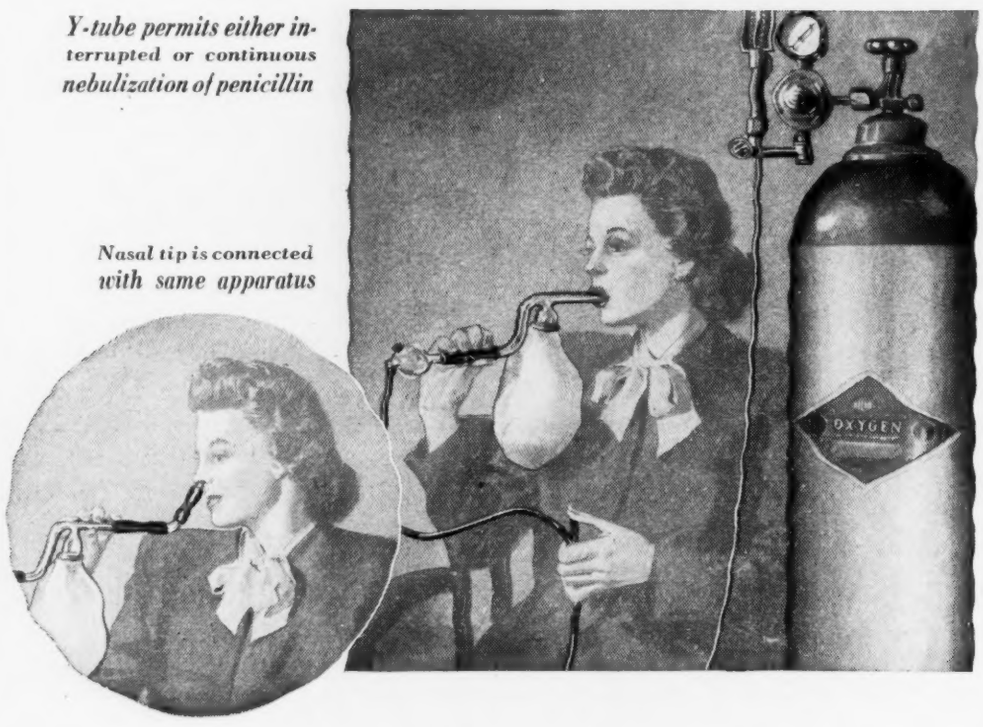


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1. Human Fertility, 10:25, March, 1945.

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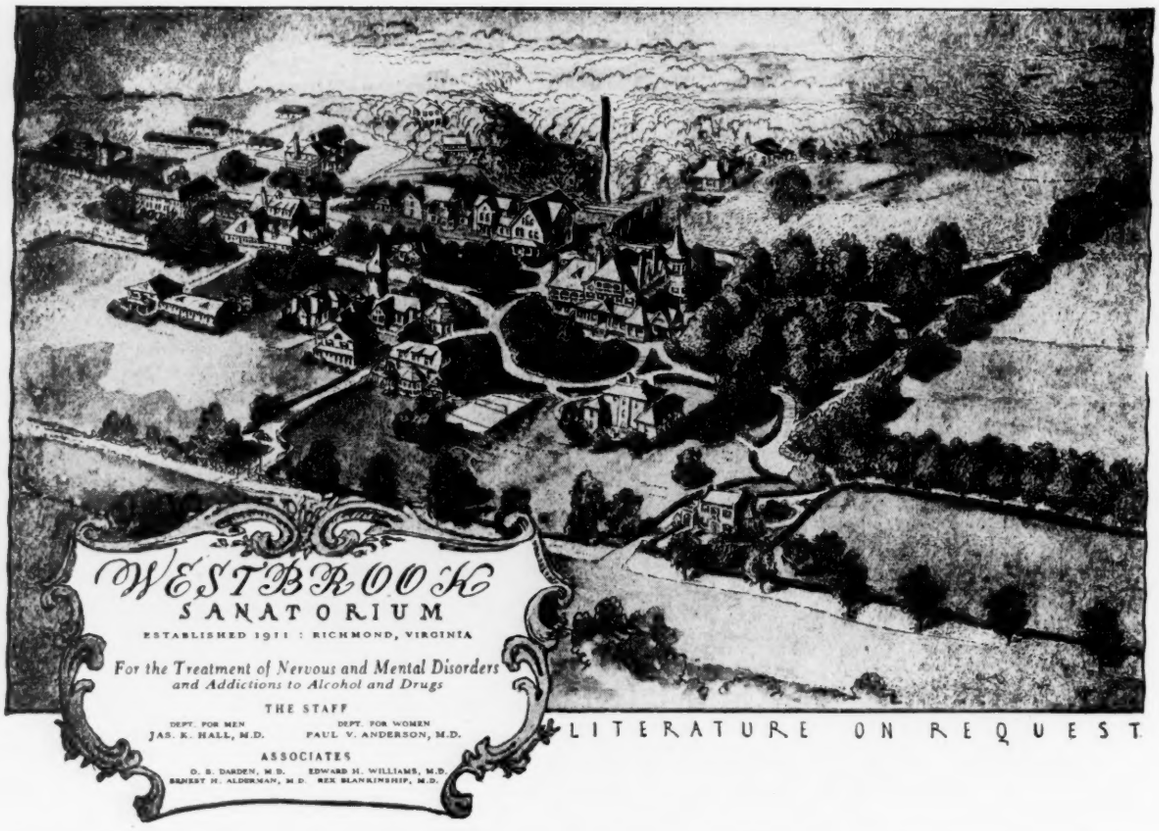
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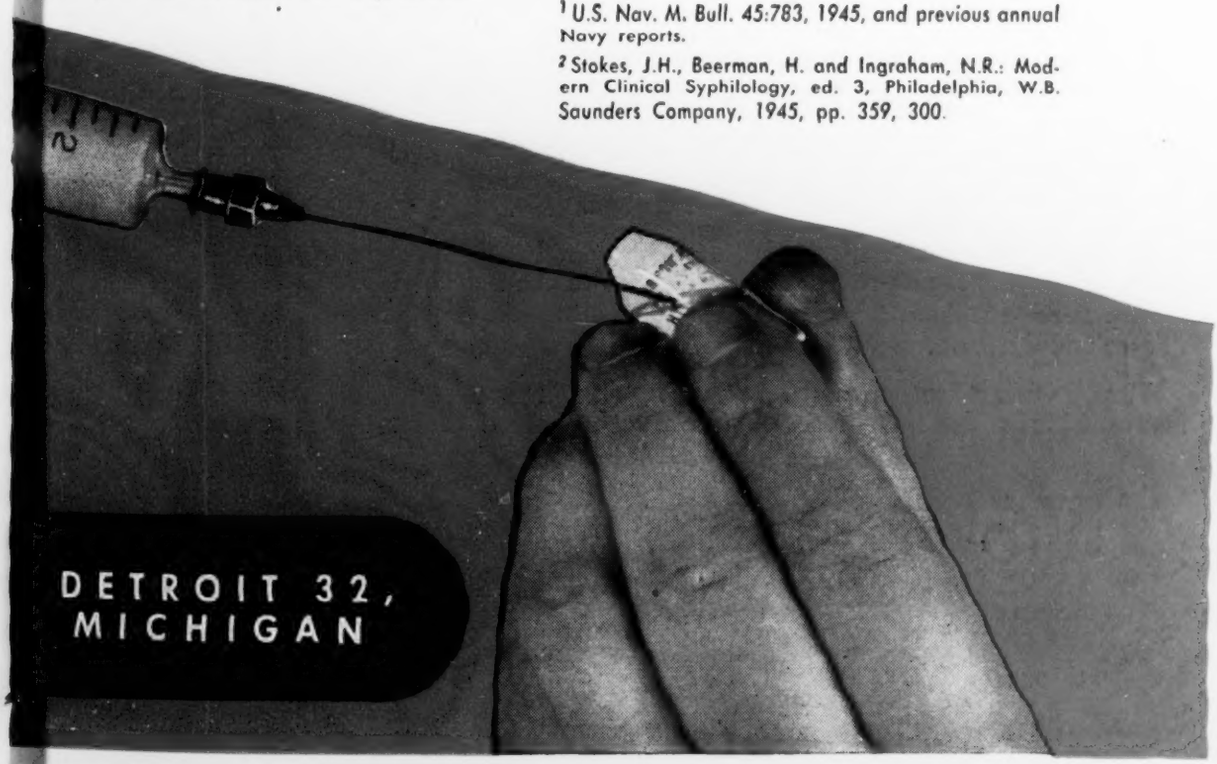
[1] U.S. Nav. M. Bull. 45:783, 1945, and previous annual Navy reports.

[2] Stokes, J.H., Beerman, H. and Ingraham, N.R.: Modern Clinical Syphilology, ed. 3, Philadelphia, W.B. Saunders Company, 1945, pp. 359, 300.



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# Old Way . . .

## CURING RICKETS in the CLEFT of an ASH TREE

FOR many centuries,—and apparently down to the present time, even in this country—ricketic children have been passed through a cleft ash tree to cure them of their rickets, and thenceforth a sympathetic relationship was supposed to exist between them and the tree.

Frazer* states that the ordinary mode of effecting the cure is to split a young ash sapling longitudinally for a few feet and pass the child, naked, either three times or three times three through the fissure at sunrise. In the West of England, it is said the passage must be "against the sun." As soon as the ceremony is performed, the tree is bound tightly up and the fissure plastered over with mud or clay. The belief is that just as the cleft in the tree will be healed, so the child's body will be healed, but that if the rift in the tree remains open, the deformity in the child will remain, too, and if the tree were to die, the death of the child would surely follow.

*Frazer, J. G.: The Golden Bough, vol. 1, New York, Macmillan & Co., 1923

*It is ironical that the practice of attempting to cure rickets by holding the child in the cleft of an ash tree was associated with the rising of the sun, the light of which we now know is in itself one of Nature's specifics.*

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